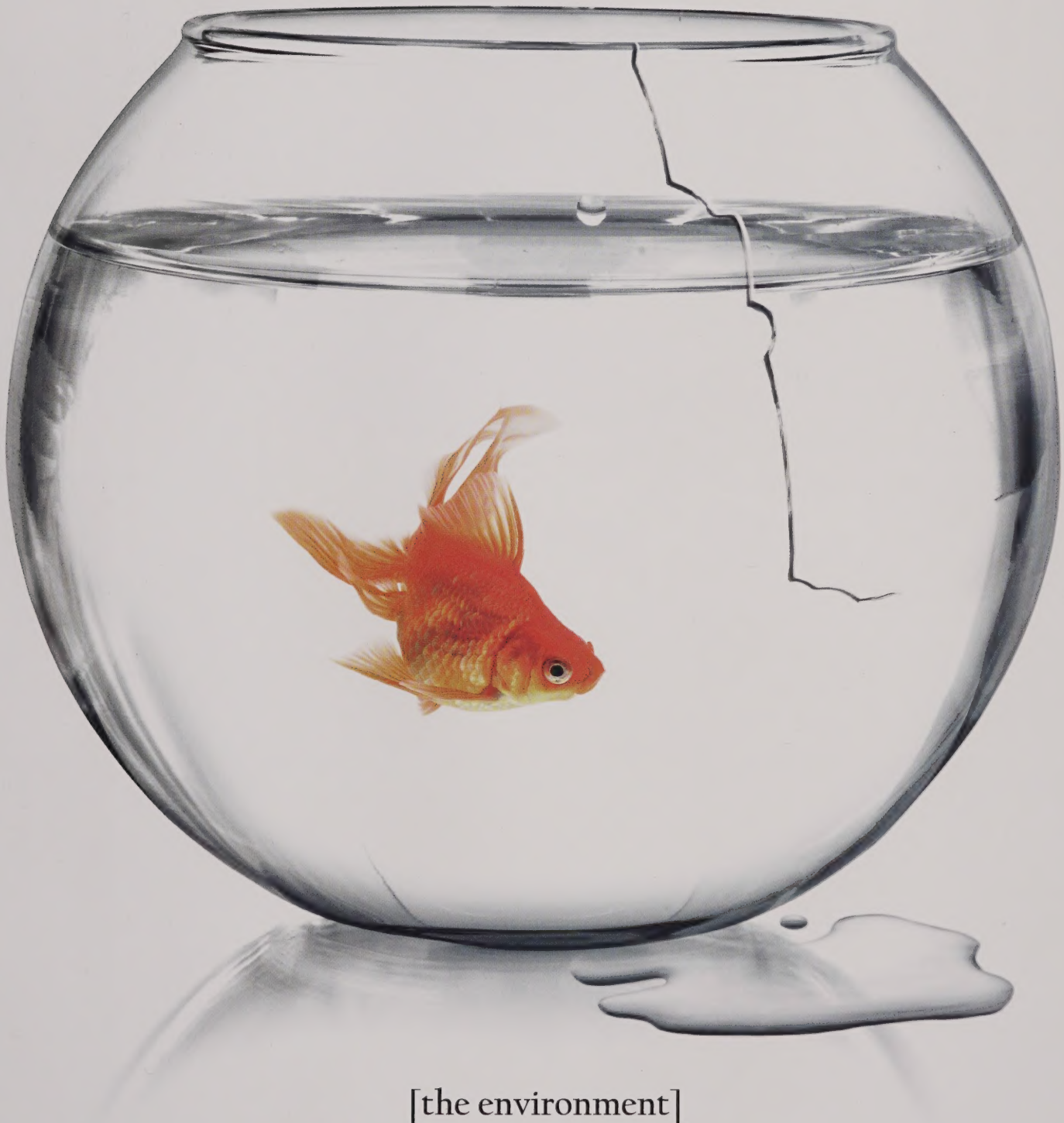
HarvardMedicine

AUTUMN 2017



[the environment]

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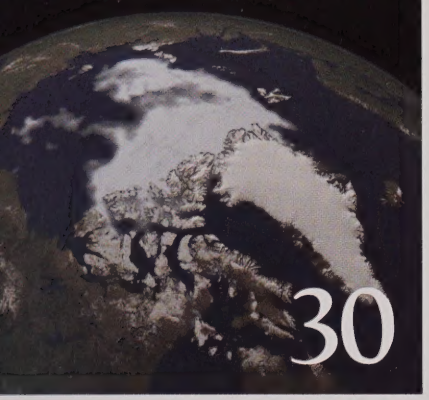
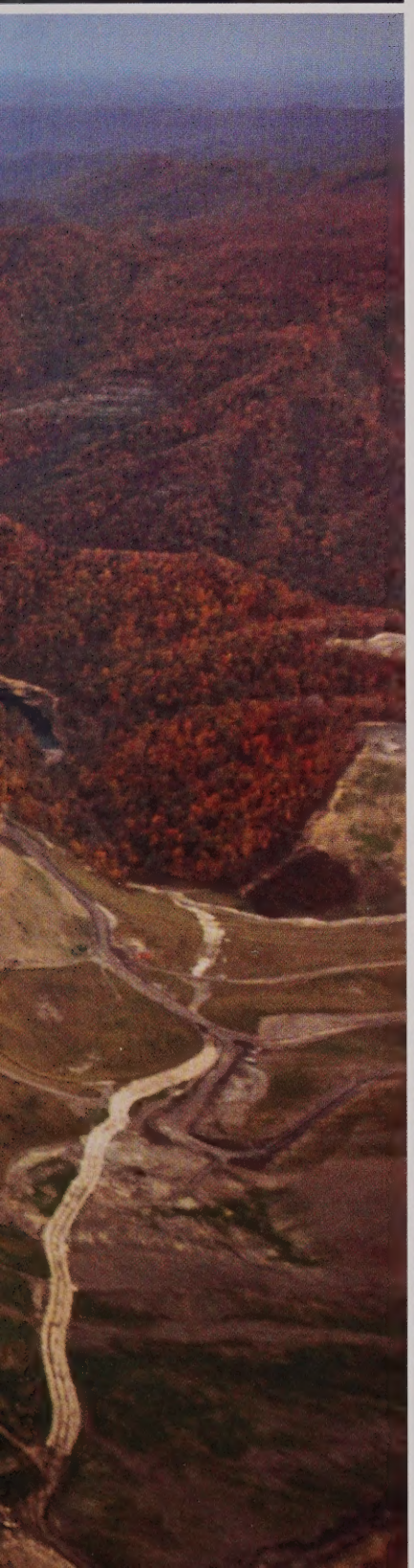
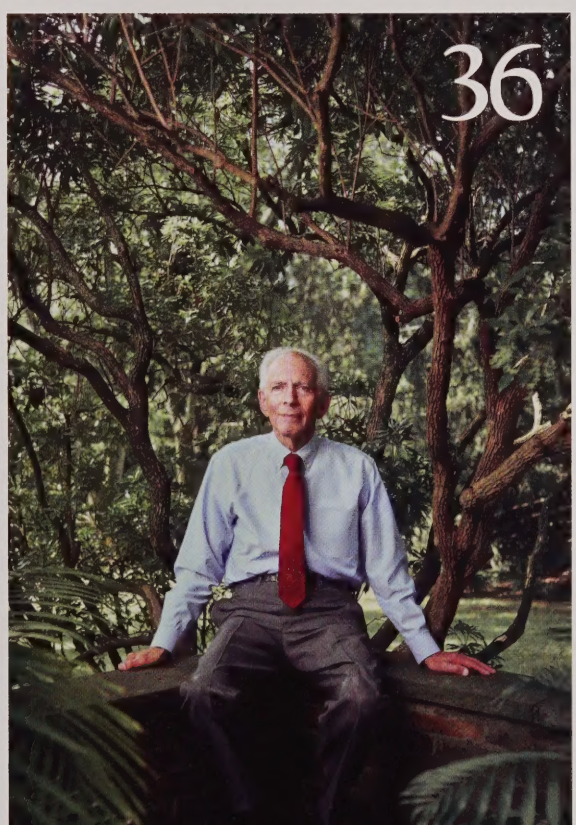
MATTIAS PALUDI (COVER); PAUL CORBIT-BROWN





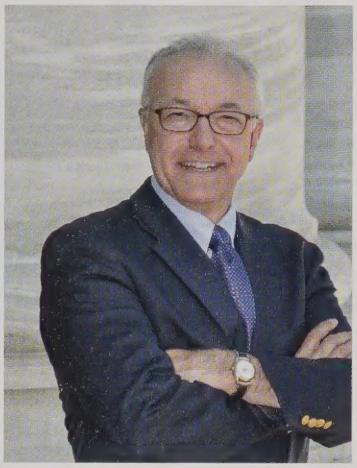
Special Report: The Environment



Feature

Departments

From the Dean



THESE ARE CHALLENGING TIMES for those of us in the medical profession.

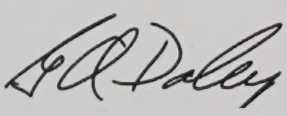
The earth is in jeopardy, and we are losing the right to live in a safe, healthy environment. Air filled with harmful aerosols travels far from where its pollutants originated. Contaminated water—ground, surface, and sea—harms people and food supplies. Catastrophic weather causes illness, damage, and death, and emphasizes the cost of a changing climate. And the health burdens that lead and other industrial emissions cause for young children remind us that hazardous chemicals in the soil on which we work, play, and live can bring lifelong grief.

This month, the *Lancet* Commission on Pollution and Health released the first-ever analysis of the global effects that all forms of pollution—air, water, soil, and occupational—have on human health and productivity. The commission's report pulls no punches. Led by Philip Landrigan '67, dean for global health at the Icahn School of Medicine at Mount Sinai, and Richard Fuller, president of Pure Earth, forty international experts on health and the environment assessed pollution's effects and found that "pollution is now a substantial problem that endangers the health of billions, degrades the Earth's ecosystems, undermines the economic security of nations, and is responsible for an enormous global burden of disease, disability, and premature death."

The authors report that in 2015 nine million deaths—16 percent of global mortality—could be attributed to pollution worldwide. The situation is even more dire for people living in low- and middle-income countries. In those regions, pollution accounted for 25 percent of deaths.

The report's authors are blunt: Pollution, climate, and the health of Earth's human civilizations and its natural systems are inextricably linked. We are all at risk.

These are sobering findings requiring action. We physicians spend our lives protecting the health and well-being of our patients. As assaults on our environment escalate, we must act to protect the planet that we call home. Inaction—or insufficient action—will cause harm. We cannot allow that to happen.



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Dean of Harvard Medical School

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STEVE LIPOFSKY

Letters to the Editor

CHART NOTES FROM OUR READERS

Fathers and Sons

I thought the Spring 2017 issue of *Harvard Medicine*, with its articles on the important issue of rural health, was fascinating. For me, however, the article on John Coltrane touched on an area—music—in which I have more than a passing interest.

My eldest son, Peter, has long written about American roots music—blues, country, and rock and roll—and on musicians key to its development, such as legends Sam Cooke, Elvis Presley, and Robert Johnson. Music is very much a part of the life of my younger son, too. Tom is a jazz musician and the founder and executive director of a performing arts organization in Albuquerque. Ravi Coltrane, one of John's sons, was the featured performer at the 12th Annual New Mexico Jazz Festival, which Tom organized.

I sent the Coltrane article to Tom and am saving the issue for Peter.

WALTER GURALNICK DMD '41
CAMBRIDGE, MASSACHUSETTS

Editor's note: We received this letter shortly before Dr. Guralnick's death. We are honored to have received it and to share it.

It Takes a Village

The Spring 2017 issue of *Harvard Medicine*, "Is rural health care out of reach?" presents both a comprehensive analysis of the problems U.S. rural residents face when they try to obtain adequate medical care and a glimpse into the many innovative steps being taken by Harvard-affiliated researchers and providers to improve the situation.

These problems are not prevalent only in the wide-open spaces of the West and Alaska. I've seen this problem firsthand in the Cooperstown region of New York, where I've been a member of the Bassett Medical Center/Bassett Healthcare Network for more than five decades.

Most of rural upstate New York continues to have a weak economic backbone requiring ever-creative health care solutions. Bassett's survival has always been economically tenuous; the economy of its catchment area has lagged more than in much of upstate New York, let alone downstate. Otsego County, with the village of Cooperstown as its county seat, is in the federally designated region of Appalachia. With the decline of viable farming and manufacturing in upstate New York, most of the area has continued to scrape by economically. Cooperstown and nearby Oneonta, home to Hartwick College and the State University of New York at Oneonta, however, remain vibrant.

I'm convinced that the Bassett system has remained viable since its founding in 1922 because it has never been afraid to try new ideas. Mary Imogene Bassett, for example, the hospital's inaugural chief of the medical staff, was possibly the first female physician to earn such an appointment in this country. Following her death, a group of physician-leaders turned the hospital into an academic hospital centered in a village of approximately 2,000 inhabitants. The concept of the rural academic center, combined with the charm of Cooperstown, attracted two rising academic stars from Columbia University Medical Center: surgeon James Greenough and internist George Miner Mackenzie. Young physicians from Columbia, Harvard, and elsewhere followed. Hospital leadership established a full-time salaried staff model, highly unusual for the day, and, in 1932, produced a plan for prepaid medical care, which served a portion of Bassett's patients through the Great Depression and World War II.

Beginning in the 1970s, Bassett gradually established clinics in an eight-county area around Cooperstown, thus becoming the dominant health care provider for a large proportion of the residents living in the approximately 5,600-square-mile area bounded by Albany Medical Center and its clinics to the northeast, Utica hospitals and clinics to the north, Upstate Medical Center and clinics in Syracuse to the northwest, United Health Services in Johnson City adjacent to Binghamton to the southwest, and an indistinct border in the northern Catskill Mountains to the south.

When I retired in 1995, I worked with Bassett's director of research to lay the groundwork for a regional telemedicine system. Twenty-two years later, we have a system that links Bassett's six hospitals, thirty-three clinics, and twenty school-based health centers.

Currently, Bassett is an accountable care organization attempting to shift from a fee-for-service model to a preventive medical-home model. Profound uncertainties loom, however, over the potential economic effects on health care by the present political leadership in Washington.

In 2010, the hospital's evolving relationship with the College of Physicians & Surgeons of Columbia University led to the development of a separate medical application track—the Columbia-Bassett Program—which allows students in that track to spend their first two years of medical school centered in Washington Heights and their last two years centered in the Bassett Healthcare Network.

I've had the pleasure of researching this history of the Bassett system while writing my recently published book, *Bassett Hospital in Cooperstown NY: 200 Years of Health Care in Rural America*, an eight-year labor of love. I remain active in the Bassett community; in addition to being a founding member of the Bassett Medical Alumni Association, I'm an attending physician and director of medical education emeritus in the Bassett Healthcare Network and a clinical professor emeritus of medicine in the College of Physicians & Surgeons of Columbia University.

JOHN S. DAVIS '56
COOPERSTOWN, NEW YORK

Apology Department

The Spring issue of *Harvard Medicine* included the letter "Giving Due." The letter indicated that Jonathan C. Horton '80 had been a graduate student of Steve Kuffler's. In fact, Horton was not Kuffler's graduate student. We regret this error.

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*Harvard Medicine welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *107 Avenue Louis Pasteur, Suite 111, Boston, MA 02115) or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length and clarity.*

FAMILIAR FACE, NEW ROLE

Lisa Muto appointed executive dean for administration

AFTER SERVING as interim executive dean for administration since late last year, Lisa Muto was named HMS executive dean for administration in June. Muto has been a part of the Harvard community for nearly three decades. Her knowledge of the School and her commitment to its mission are but two of the many reasons she was chosen for the position, said HMS Dean George Q. Daley '91 in a letter announcing the appointment.

"From the outset, I was greatly impressed by Lisa's remarkable intelligence, strategic approach to problem solving, and vast knowledge of the School's priorities and culture," wrote Daley, further noting her "managerial skills, her tenacity, and her candor."

"Lisa," he added, "is deeply devoted to HMS."

In her new role, Muto will manage the School's vital administrative functions and will partner with members of the HMS community to advance the excellence of the School's scientific and educational missions. Her immediate priorities include assembling an administrative team and working to ensure the School's long-term financial health.

Muto brings to these responsibilities a significant depth of experience in operations and strategic planning. She joined HMS as a senior administrative and financial officer in the Department of Health Care Policy, and, for the past nine years, has served as the associate dean for institutional planning and policy, advancing academic and strategic planning for the preclinical departments.

Muto was instrumental in launching the Department of Biomedical Informatics, was a key player in the development of the School's continuing medical education program, and, in 2011, co-led the School's successful Liaison Committee on Medical Education accreditation process.

Muto has served as a co-chair of the HMS Joint Committee on the Status of Women and is a member of the HMS Task Force on Diversity and Inclusion. In 2007, she was honored with the Joseph B. Martin Dean's Award for Leadership in Advancement of Women Staff. She earned her AB magna cum laude from Harvard College and her PhD from McGill University.

"I am honored Dean Daley has offered me this opportunity to shepherd HMS in the coming years," said Muto. "I share his enthusiasm for the School and for the members of this remarkable community, and I will partner with him to foster an inclusive, transparent, and supportive environment where people are empowered to do their best work."

Members of the Class of 2021 visited Boston neighborhoods during their first week on campus. One of the tours was guided by Jennifer Bennet (far right), executive director of a Boston-based mobile health service.

Taking It to the Streets

Members of the Class of 2021 learn the importance of community

THREE DAYS AFTER ARRIVING ON CAMPUS, members of the Harvard Medical School and Harvard School of Dental Medicine Class of 2021 fanned out across Boston. Their task: get to know the people and the communities they will be serving. The outing was the first of its type in the School's 234-year history.

In small groups, students walked or took public transportation to one of twenty different neighborhoods. There, they met with leaders from local organizations, such as Urban Edge, Boston Health Care for the Homeless, and the Margaret Fuller Neighborhood House, to learn about the communities that some of their future patients call home.

"Your patients do not live inside your hospital," Nancy Oriol '79, faculty associate dean for community engagement in medical education at HMS, told the students. "We all come from someplace else, and we bring that reality to the doctor's office."

In Roxbury's Dudley Square, students were introduced to the history and needs of a community in one of Boston's Black culture centers.

"I was so surprised at how close this neighborhood was to HMS and how there is such a distinct difference in the population that lives here," said Ayotomiwa Ojo, a first-year HMS student from Lima, Ohio.

Guided by Jennifer Bennet, executive director of The Family Van—a mobile health service that provides access to health care for people living in some of Boston's more underserved communities—Ojo's group toured important local centers and historical sites, discussed health care challenges faced by residents, and witnessed the changing landscape of a neighborhood struggling with gentrification and uncertainty.

After spending an afternoon in various neighborhoods, the first-year students returned to the HMS Quad and discussed their experiences.

"Zip code is as strongly associated with health as genetic code," said Oriol. "Learn what your patient's world is about, learn from them how you can best help them help themselves."

The HMS Class of 2021 has nearly equal numbers of women and men, and individuals range in age from 21 to 31. One-third report Asian or Asian-Indian heritage and one-fifth identify as minorities underrepresented in medicine. Nearly 7,000 applicants yielded a final class of 165.

Students in the class come from thirty-six U.S. states and four countries outside the United States: Canada, Italy, Rwanda, and Turkey.

For new students, these first few days represented the beginning of a lifelong journey of not just learning, but learning how to learn—from each other, from teachers, and, most important, from patients.

—Kevin Jiang and Susan Karcz

BENCHMARKS

DISCOVERY AT HARVARD MEDICAL SCHOOL

MIND'S EYE

Visual system blueprint may be present at birth

For decades, researchers have known that the primate brain is organized into "maps" corresponding to each sense: one of the body for touch, one of the visual world for sight, and one of tones for hearing. In adult primates, these maps are divided into distinct areas responding to different classes of stimuli in each of the senses. Whether this organization is innate or develops over time through experience has been a mystery.

A study published July 3 in *eLife* by HMS researchers Michael Arcaro and Margaret Livingstone suggests that both could be true.

The research team's findings reveal that a primitive blueprint of brain organization is present in primates just a few days after birth and appears to gradually fill in with age and experience.

The findings, the scientists say, may explain some features of neurodevelopmental disorders such as autism, which often involve avoidance of certain visual stimuli.

Livingstone, the HMS Takeda Professor of Neurobiology, has long worked to decipher organization in the brain's visual system. In the current work, she and Arcaro studied the visual system in four macaques as young as 10 days by monitoring their brain activity with functional magnetic resonance imaging as the animals viewed various images, including scenes and faces.

Arcaro, a postdoctoral fellow in Livingstone's lab, analyzed all the data, even those gathered while the animals were asleep, and made a surprising finding: Even when the animals were asleep, multiple parts of the visual system would turn on in conjunction with one another, a finding that suggests a functional organization that connects all vision-associated areas.

The researchers worked with the same macaques for several years, scanning their brains periodically as the animals matured. The investigators found that the primitive maps remained but that they gradually filled in and became more sophisticated, capable of responding to stimuli that weren't in the primates' environment at birth.

The young macaques' visual system activity already appeared to be organized for object recognition and visually guided actions. They also had so-called retinotopic organization, with different areas of the visual system becoming active in response to input from various parts of the retina's visual field.

They were, however, missing certain hallmarks early in life that were prominent in the same monkeys as they aged. They lacked, for example, clusters of neurons in the fusiform gyrus—a structure linked to recognition, among other functions—corresponding to visual stimuli from faces. Such neuronal selectivity arose as the macaques reached about 200 days of age.

Given the close genetic relationship between macaques and people, the findings, the researchers say, have implications for humans. The fact that the visual system does not later incorporate and respond to stimuli such as faces, they add, could explain some of the aberrations seen in neurodevelopmental disorders, including an aversion to looking at faces, a common feature in people with autism-spectrum disorders.

The new findings also underscore the importance of correcting any visual deficits present at birth to ensure the proper development of higher visual and cognitive functions. *—Christen Brownlee*

The Power of Calm

Curbing inflammation shown to cut risk of heart attack, stroke

THE RESULTS OF A TWENTY-FIVE-YEAR CLINICAL TRIAL on reducing cardiovascular risk show that, among people who have had a heart attack, reducing inflammation can significantly reduce the risk of recurrent heart attacks, strokes, and cardiovascular deaths. Study participants received a targeted anti-inflammatory drug that lowered inflammation but had no effect on cholesterol.

Investigators from HMS and Brigham and Women's Hospital reported the results in the August 27 issue of the *New England Journal of Medicine*.

"We've been able to definitively show that lowering inflammation independent of cholesterol reduces cardiovascular risk," says Paul Ridker '85, an HMS professor of medicine, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's, and lead author of the study.

The study was sponsored by Novartis Pharmaceuticals, maker of canakinumab, the monoclonal antibody used in the study. The drug targets interleukin-1ß.

The researchers enrolled more than 10,000 patients who previously had a heart attack and had persistent elevated levels of high sensitivity C-reactive protein, a marker of inflammation. All patients in the trial received aggressive standard care, including high doses of cholesterol-lowering statins.

Participants were randomized to receive 50, 150, or 300 milligrams of canakinumab, or a placebo, and were followed every three months for up to four years.

The team reported a statistically significant 15 percent reduction in risk of a cardiovascular event, including fatal or nonfatal heart attacks and strokes, for patients who received the 150-milligram dose of canakinumab. In addition, the need for interventional procedures, such as bypass surgery and angioplasty, was cut by more than 30 percent; these reductions were above the reduction in risk realized from taking statins alone. No effect was observed for the lower 50-milligram dose.

Participants with greater-than-average reductions in the inflammation marker had a nearly 30 percent reduction in the risk of a recurrent heart attack, stroke, or cardiovascular death. These data , say the authors, show the importance of targeting treatment with canakinumab to those in greatest need, while sparing patients who may not benefit as much the adverse side effects.

—Haley Bridger

Salpingoeca rosetta

COURTESY OF ARIELLA WOZNICA, NICOLE KING LAB, UNIVERSITY OF CALIFORNIA, BERKELEY

The Birds and the Bees

"Bacterial aphrodisiac" triggers cell mating, illuminates multicellular evolution

THE RESEARCHERS WERE SIMPLY SEEKING bacteria that would stimulate *Salpingoeca rosetta* to form the rosette-shaped colonies that give them their name. What they found was a bacterium that motivated *S. rosetta* to have sex.

"The last thing anyone expected was an aphrodisiac," says Jon Clardy, the Hsien Wu and Daisy Yen Wu Professor of Biological Chemistry and Molecular Pharmacology at HMS.

The discovery, published August 31 online in *Cell*, is the first known instance of bacteria-induced mating in eukaryotes, organisms with membrane-enclosed nuclei and other organelles. The finding may provide insight into broader questions of how bacteria influence the development and behavior of all eukaryotes, including plants and animals.

"An appreciation of the importance of symbioses with bacteria, such as the microbiome, is growing," says J. P. Gerdt, a research fellow in the Clardy lab and co-first author of the study, "but I had never heard of anything like a bacterium that induces sexual fusion."

The study also revealed that the primitive *S. rosetta*, which are single-cell saltwater dwellers that are the closest living relatives of animals, can make chondroitin, a molecule scientists thought arose much later in the evolutionary tree.

For the current work, Nicole King of the University of California, Berkeley, who shares senior authorship with Clardy on the study, added the bioluminescent marine bacterium *Vibrio fischeri* to dishes of *S. rosetta*, hoping to trigger rosette formation. But no rosettes formed. Instead, the tiny *S. rosetta* flagellates propelled themselves into swarms of up to 50 cells each—and began to mate.

What caused this to occur? Tests in Clardy's lab narrowed the candidates to a single protein not previously known to science. The researchers dubbed it EroS, short for Extracellular regulator of Sex.

Further experiments revealed that EroS is a chondroitinase—an enzyme that breaks down chondroitin. When the researchers peered deeper, they found that *S. rosetta* makes chondroitin sulfate, a chain of sugars best known for forming part of the structure of cartilage. The serendipitous discovery changes the evolutionary timeline of chondroitin development.

The researchers think their work could illuminate the evolutionary history of bacterial symbioses and help them gain a deeper understanding of how humans are affected by bacteria today.

—Stephanie Dutchen

THE HIDDEN, REVEALED

South Asian genomic analysis could inform disease prevention

A NEW GENOMIC ANALYSIS reveals how populations in South Asia—including people living in Bangladesh, India, Nepal, Pakistan, and Sri Lanka—are particularly vulnerable to rare genetic diseases.

Several diseases specific to South Asian populations have previously been identified, but the genetic causes of the vast majority have remained largely mysterious. A multi-institutional study, led by researchers at HMS and the CSIR-Centre for Cellular and Molecular Biology in Hyderabad, India, reveals that so-called founder effects, in which a small number of ancestors give rise to many descendants, significantly contributed to the high rates of population-specific, recessive diseases in the region. The work appeared online July 17 in *Nature Genetics*.

"Our work highlights an opportunity to identify mutations that are responsible for population-specific disease and to test for and decrease the burden of recessive genetic diseases in South Asia," says David Reich, an HMS professor of genetics and co-senior author of the study.

The researchers analyzed genome-wide data from more than 2,800 people within upwards of 260 South Asian subgroups. They found that nearly one-third of these subgroups derived from distinctive founder events.

Such founder events tend to limit genetic diversity. Geographic, linguistic, or cultural barriers, such as restrictions on marriage between groups, increase the likelihood that mates share much of the same ancestry. This can lead to the perpetuation and proliferation of certain rare, recessive diseases.

"Everybody carries a small number of mutations that could cause severe disease, but each person usually only has one copy. Two copies are needed to get sick," says the study's first author, Nathan Nakatsuka, a graduate student in Reich's lab. "If parents share a common ancestry, there is a greater risk that they will carry the same recessive mutation, so their offspring are at much greater risk of inheriting the two copies needed to manifest disease."

The prevalence of these genetic variants increases disease risk—and makes them easier to detect.

Fourteen of the groups identified are made up of more than 1 million people, according to census data. Discoveries stemming from rare disease research in these populations could affect large swaths of people in South Asia.

Studying these variants may highlight the mechanisms causing disease, which could lead to new treatments.

Patan, Nepal

Clostridium botulinum

Deadly Increase

New type of botulinum toxin found

THE FAMILY OF NERVE-DAMAGING TOXINS produced by *Clostridium botulinum* is so deadly it is classified as one of the most dangerous potential bioterrorism agents. Although botulism, the illness the toxins cause, is rare, it can paralyze and kill.

There are seven known types of botulinum toxin produced by various *C. botulinum* strains, designated by the letters A through G. Toxins A and B, identified in 1919, are used therapeutically to control muscle spasms, chronic pain, and overactive bladder, and cosmetically to smooth wrinkles. In 1969, toxin G was discovered, and, in 2013, there was a brief flurry of interest over what seemed to be the discovery of type H. Gene sequencing, however, showed it to be a combination of a subtype of toxin F and a piece of toxin A.

There is now, however, new cause for interest. Min Dong, an HMS assistant professor of surgery at Boston Children's Hospital, and colleagues have reported a new botulinum toxin. Provisionally called toxin X, it has properties that set it apart from its cousins. The study appeared August 3 in *Nature Communications*.

"Sequence-wise, it doesn't look like any other toxin," says Dong, "and it cannot be recognized by antibodies to any other known botulinum toxin."

Dong's team showed that botulinum toxin X cleaves the same set of nerve proteins targeted by other botulinum toxins but that it also cleaves a group of proteins that none of the other toxins touch. These proteins are poorly characterized, so toxin X may be a tool that researchers can use to better define the proteins' functions. These additional protein targets might endow toxin X with new, medically relevant properties.

Since each toxin requires a separate antibody to neutralize it, learning of this new botulinum toxin may allow doctors and researchers to better defend against botulism. *—Nancy Fliesler*

JAMES CAVALLINI/PHOTO RESEARCHERS; BSIP/PHOTO RESEARCHERS (FAR RIGHT)

Behavioral Analysis

Molecular tests beat standard lab cultures in predicting tuberculosis treatment outcomes

NOVEL MOLECULAR TESTS are gaining popularity as a rapid way to detect genetic mutations that render tuberculosis impervious to drug treatment. Yet, how well these new tests gauge the risk of actual drug failure and patient death has remained unclear.

Now, research led by HMS scientists shows that when it comes to predicting response to treatment and risk of dying, molecular tests that detect resistance to a class of tuberculosis drugs known as fluoroquinolones may be as good as, and even superior to, traditional drug-sensitivity tests conducted in lab cultures. The study was published August 3 in *Clinical Infectious Diseases*.

Traditional drug-sensitivity tests can take up to eight weeks to yield results. By comparison, point-of-care molecular tests provide results within hours, expediting treatment decisions.

Past research has indicated, however, that molecular tests may fail to detect resistance mutations in more than 30 percent of strains insensitive to the drug moxifloxacin. This failure rate has fueled anxiety about their reliability as resistance detectors.

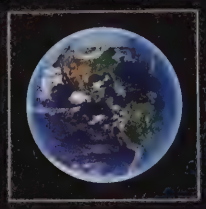
"Culture-based testing is still considered the gold standard for diagnosing TB resistance," says Maha Farhat, an HMS assistant professor in the Department of Biomedical Informatics and lead author of the study. "However, our results should provide reassuring evidence that molecular tests are just as reliable, if not better, in predicting overall treatment outcome as a result of such resistance-causing gene alterations in patients who fail treatment with fluoroquinolones."

The researchers caution that their study involved only 171 patients and that further research is needed to reveal the predictive accuracy of molecular versus standard lab tests in other forms of drug-resistant tuberculosis.

The investigators add, however, that the data provide compelling evidence that molecular tests could become a mainstay in informing drug choice and predicting the clinical course of a patient's infection.

"Widespread implementation of molecular tests to guide regimen development is critical to stemming transmission of, and illness and death due to, drug-resistant forms of tuberculosis," says Carole Mitnick, an HMS associate professor in the Department of Global Health and Social Medicine and the study's senior investigator. *—Ekaterina Pesheva*

Pulmonary TB, colored x-ray



The Power of Nature

THE MILLIONS WHO GATHERED to watch the August solar eclipse were carrying on a tradition of fascination with this natural phenomenon that written records indicate goes back at least four thousand years. Yet the excitement those viewers felt is of relatively recent vintage.

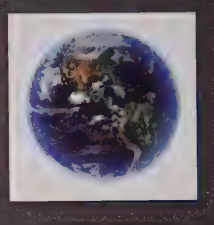
"Eclipse" stems from the Greek word for abandonment, and for many of the ancients, the solar eclipse was indeed something to fear. Considered a visitation of angry gods and a harbinger of evil, people would pray, weep, or yell at the darkening sun, while shooing pregnant women to places of hiding, the better to protect unborn children from blindness, cleft palate, or birthmark.

Yet, there were some, the curious, the seekers, who sought a greater understanding. Those early scientists observed and measured. They then built instruments that improved observation and measurement—and allowed prediction. One such tool, the Antikythera mechanism, was used to calculate celestial movements with a stunning degree of accuracy. That small device, and subsequent tools, helped clear away the clutter of myth, allowing humans to better understand the rules by which Nature behaves.

Today, scientists continue the tradition of observing and measuring, gathering data that give context to seemingly disparate phenomena: wildfires and respiratory problems; drought and cardiovascular disease; warming temperatures and upticks in infectious disease agents and toxic algae blooms. With amazing accuracy and scope, we can document and track environmental changes that affect our lives—and the life of our planet.

We talked with biomedical researchers at HMS who study the environment and its effects on us. And we explored what physical scientists are learning about our effects on the environment. The news is not good. We are abusing our world, and, by extension, ourselves. Preventive measures are available, they tell us. We need to apply them.


inherit
the
wind



Changes in Earth's climate are hurting our health and may well be dashing our hope to coexist peacefully

by Stephanie Dutchen

The morning sun dimmed over Boston, and dust sifted down from the hazy yellow sky. At first people thought that what they were seeing was smoke and ash from a forest fire, but the *Boston Daily Globe* soon reported it was the last gasp of a storm that had whipped up more than 300 million tons of dirt from the Great Plains. ■ In New England, that May 1934 event was largely a novelty. But it was a grim reality from Texas to North Dakota, where thousands of people were suffocating on the fine, dry soil buffeted about by that dust storm and the hundreds of others that had pummeled the heart of the country for a decade. The wracking coughs, fevers, and body aches of "dust pneumonia," a form of silicosis that clogs and irritates the lungs, killed some within days, particularly children and older adults, and left others debilitated for life. ■ Accounts such as *The Worst Hard Time*, written by *New York Times* columnist Timothy Egan, describe in heartbreaking detail how unsustainable farming practices, exacerbated by an eight-year drought, led to not only ecologic and economic devastation but also a flurry of health problems. People became malnourished and depressed. Eye, sinus, throat, and bronchial infections abounded. Measles and influenza swept through towns. Wind-driven dirt, lodged under eyelids, abraded corneas and caused blindness. Injuries and deaths from vehicular accidents spiked as visibility often dipped to near zero. Surgical facilities closed as dust pressed in.

The health consequences of the Dust Bowl are gaining new notice as experts on climate change predict that with increases in temperature and shifts in rainfall patterns, the world's populations can expect more pervasive and intense droughts, and larger, more frequent dust storms. Dust storms, including intense ones called haboobs, doubled in the U.S. Southwest between the 1990s and early 2000s, leading to a surge in dust-related fatal car accidents, in respiratory ailments such as asthma, and in valley fever, caused by breathing in fungus stirred up from desert soils.

And it's not just dust. Nearly all facets of climate change, from warming and rising seas to escalating extreme weather events, are damaging human health and behavior. In the United States alone, in the late summer and early fall of this year, West Coast residents experienced chart-topping temperatures and massive wildfires that caused widespread heat exhaustion and breathing difficulties and killed dozens. The series of hurricanes that struck the Gulf Coast and the Caribbean killed more than one hundred people and caused untold illnesses, including some among low-income residents who couldn't afford to leave their mold-infested apartments after floodwaters receded or didn't have access to safe drinking water for weeks.

Variables compound and complicate one another, sometimes in unexpected ways, and although vulnerable populations will continue to be disproportionately burdened, it's becoming more difficult to find any place in the world where physical or mental health remains unassailed by changes in Earth's climate.

Dominoes

"Climate change is a significant threat to the health of the American people," begins *The Impacts of Climate Change on Human Health in the United States: A Scientific Assessment*, a 300-page report compiled by thirteen government agencies in 2016.

The report's authors join other scientists in warning that changes to the climate will exacerbate environmental phenomena that put human health at risk. They say that natural disasters and the health hazards that accompany them will increase in frequency and severity, expand into new geographic areas, and strike at unprecedented times of year.

Some of these events directly affect health. People die during and after hurricanes, tornadoes, wildfires, floods, droughts, heat waves, deep freezes, and wild temperature and precipitation swings. Others are injured, fall ill, or get sicker, or are displaced, stressed, or traumatized. Air and water quality worsen while food and water availability decrease, provoking conditions such as asthma, cardiovascular stresses, malnutrition, and diarrheal illnesses.

Other health consequences may be less immediately apparent. Anthropogenic factors can affect health even as, or before, they influence changes in the climate. Higher concentrations of atmospheric carbon dioxide nourish plants that then release more allergens. Deforestation brings humans and animals into new or sustained contact that can spawn more cases of known or novel zoonotic diseases.

"We're heading toward ecological disaster," says Megan Murray '90, the Ronda Stryker and William Johnston Professor of Global Health at HMS, director of the research core in the HMS Department of Global Health and Social Medicine, and a professor of epidemiology at the Harvard T.H. Chan School of Public Health. "It's hard to even think about it as a health issue when we're confronting the possibility of the destruction of our life on Earth."

Known Unknowns

"In studying infectious disease, we usually focus our efforts on the fundamental biology of infectious agents, clinical care, and outbreak response," says Pardis Sabeti '06, a professor at Harvard University and at the Harvard Chan School and an institute member of the Broad Institute of Harvard and MIT. "Yet the history of the human genome reveals to us that one of the strongest pressures on human populations is a changing environment."

Biomedical researchers are trying to close knowledge gaps in how humans are affected by changes in our environment and which health interventions work best. They are getting better at linking individual events to climate drivers, and they're collecting data on health outcomes and constructing more accurate predictive models. But they have not yet mastered "what happens to human health and well-being when temperatures change, for example," says Nick Obradovich, an associate at the Harvard Kennedy School's Belfer Center for Science and International Affairs and at the Harvard University Center for the Environment. Doing so is necessary, he says, "so that we can determine where policy and monetary resources need to be placed, in addition to trying to prevent the worst climate outcomes."

Moving In

In September 2014, Anne Piantadosi had just started her infectious disease training at Massachusetts General and Brigham and Women's hospitals when a twenty-five-year-old man arrived with fever, rash, vomiting, and confusion. The cause: unknown.

"He was really sick and we couldn't figure out why," recalls Piantadosi, now an HMS instructor in medicine at Mass General.

Eventually, tests led to a diagnosis of encephalitis caused by Powassan virus, a rare tick-borne pathogen. Before 2013, only one case had been recorded in Massachusetts. From 2013 to 2015, however, there were eight patients diagnosed at Massachusetts hospitals.

In a 2016 paper in *Clinical Infectious Diseases*, Piantadosi and colleagues argue that although greater clinical recognition could account for a portion of the rising incidence, field observations suggest more people are becoming infected.

Piantadosi's colleague Jacob Lemieux '15, an HMS research fellow in medicine at Mass General, has watched local cases of Lyme disease and babesiosis, a malaria-like illness, climb as well. Like Powassan, these diseases are transmitted by deer ticks, also called blacklegged ticks, whose habitats are expanding in this country.

"The history of the human genome reveals to us that one of the strongest pressures on human populations is a changing environment."


Megan Murray

"There are just tons of tick-borne cases, more this season than I've ever seen," says Lemieux.

The spike coincides with rising temperatures. The winter of 2015-2016 was the mildest on record for the planet, with 2016-2017 a close second. This spring, deer ticks emerged in a balmy New England a month earlier than usual. Experts warn that they could become a year-round problem in the region for people and animals.

Many climate scientists see more than a correlation. They say warmer and wetter trends mean longer transmission seasons and broader geographic ranges for diseases spread by ticks as well as those transmitted by mosquitoes and fleas. Vector-borne diseases previously confined to the tropics, such as Zika virus disease and Chagas disease, are invading the southern United States. Bugs once confined to the South, like the lone star tick, which can transmit a lethal allergy to red meat, are creeping north, and vectors usually found in lower elevations are appearing in the mountains.

Lemieux and Piantadosi confront the problem not only in the clinic but also as postdoctoral researchers in the Sabeti lab. There, they study the biology of viruses, bacteria, and parasites to learn how humans can protect themselves beyond bug spray and long-sleeved shirts. By analyzing the genomes of *Babesia microti*, Lemieux has mapped different strains across the United States and identified genetic variants that seem to correspond to relapsing forms of the illness. Genetic sequencing is likewise helping Piantadosi understand the population structure of Powassan viruses, how they grow and change, how they cause disease, and whether specific strains infect people. Both researchers hope their findings lead to treatments, vaccines, or improvements in vector control.

"A main focus of the lab is to create tools that empower every person to understand infectious disease spread and be part of the solution if an outbreak ever emerges," says Sabeti. "This is one way of many that individuals can engage in fighting climate change."

In the meantime, there is no treatment for Powassan encephalitis. Piantadosi's patient was lucky: He recovered. Two of the other seven died and another two had lingering neurological and motor issues.

Steam Heat

In 2015, after months of toppled temperature and precipitation records, San Diego experienced the hottest week of its hottest-ever October. At nearly midnight in the apartment of Obradovich and Robyn Migliorini, then a neuropsychology graduate student, it was still in the mid-80s and oppressively humid. Migliorini sprawled like a starfish in bed, trying to cool off with a fan and a spray bottle. Obradovich lay awake beside her, sweating. Sleep was an impossibility.

They were not alone. The next morning, they noticed that classmates and colleagues were as tired and grumpy as they were. Their science radar pinged. The duo decided to combine Obradovich's research on the politics of climate change with Migliorini's psychology training, which included an interest in healthy and disordered sleep, and investigate whether changes in climate meant they were looking at a new normal for sleep.

Building on controlled sleep lab studies of ambient temperature and sleep quality, the team mined a Centers for Disease Control and Prevention database that contained 30-day sleep self-reports collected from 765,000 people between 2002 and 2011. They matched those entries with meteorological records from the respondents' locations. Their findings, published in *Science Advances* in May 2017, revealed that higher nighttime temperatures indeed disrupt sleep, especially during summer. The results took on added import in light of multiple studies showing that nighttime lows are rising faster than daytime highs.

"We don't know what sleep is going to look like in 2100," says Migliorini, who completed the research while an HMS clinical fellow in psychology at Mass General and is now a postdoctoral fellow at the Bedford VA Medical Center. "We will need to adapt, whether physiologically or technologically."

Air conditioning, although it contributes to energy use and atmospheric changes, might suffice for many in this country, but not everyone can afford it. Migliorini and Obradovich's analysis found that the sleep of lower-income people and older adults was harder hit than sleep in other groups.

Hot Under the Collar

Sleep isn't the only condition that might be altered by higher temperatures. Some researchers think instances of aggression will rise. A 2013 *Science* meta-analysis of sixty studies from various disciplines that compared behavior in normal and "extreme" climate periods found that temperature spikes and abnormally high and low rainfalls significantly boost the incidence of violent crime, domestic violence, and ethnic and civil conflict internationally. The authors wrote in the *New York Times* that a global average rise of 2 degrees Celsius could increase the occurrence of civil wars by 50 percent. Their results align with what history has long indicated: that resource scarcity caused by drought or floods drove hostile acts that collapsed some of the world's greatest civilizations.

Mental health is further assaulted wherever people are traumatized by exposure to extreme weather events. Breathing poor-quality air, including particulate matter from pollution and wildfires, has been linked to neurological and psychiatric problems. Hundred-year flooding in Baton Rouge in 2016 and New Orleans in 2017 caused further mental distress in people who had survived Hurricane Katrina in 2005.

Facing crop failure and bankruptcy, tens of thousands of farmers, most of them men, have been driven to suicide by extreme droughts in rural India and Australia over the past half-century. A study this year in *Proceedings of the National Academies of Science* calculated that for every 1.8-degree increase above 68 degrees Fahrenheit during the growing season, there are sixty-seven additional suicides per day among India's farmers. Average temperatures in that country are predicted to rise another 5.4 degrees Fahrenheit by mid century.

Only a "very small fraction" of patients living in the United States are worried enough about climate change to seek medical help, says Migliorini. She is more concerned with whether the stress of experiencing a calamitous weather event might put some people at increased risk of developing a psychiatric condition and exacerbate an existing one in others, "tipping them over into something clinically significant." She and Obradovich are currently investigating whether temperature or other weather trends contribute to depression, anxiety, or other mental health conditions.

"I think it's important for all of us in the field of psychology to think about these possible links," she says, "but it's difficult because the literature on climate change and mental health is fairly nascent and speculative." As data aggregate, she suggests that clinicians ask patients about their interactions with their environment, such as whether they own an air conditioner or work outside. "Thinking about the health-environment interaction more broadly would serve us well," Migliorini says, "whether it's directly related to climate change or not."

In addition to its potential effect on mental health, anything that causes stress, including "war, insufficient food, or uncertainty over hurricanes, would be expected to affect sleep," says Elizabeth Klerman '90, an HMS associate professor of medicine in the Division of Sleep and Circadian Disorders at Brigham and Women's Hospital. "People report that they don't sleep well after earthquakes, so you could imagine that events related to climate change would affect sleep in that way, where people don't feel safe."

Several researchers are uncovering connections between sleep disorders and psychiatric symptoms, including mania and depression. Insufficient sleep in the short and long term can blunt people's immune response to infections and vaccines; lower pain thresholds; damage mood, collaboration, and productivity; and cause a slew of other health and behavioral consequences, many of which have yet to be fully explored.

"There's a lot that's still unknown about how sleep affects physiology," says Klerman. "There are studies I want to conduct related to understanding the effects of insufficient sleep or the interaction of sleep and dermatology, psychiatry, geriatrics, gastroenterology, anything that might be affected if sleep is disturbed."


Elizabeth Klerman


Pardis Sabeti


Nick Obradovich (left) and Robyn Migliorini

Sleep isn't the only condition that might be altered by high temperatures. Some researchers think instances of aggression will rise.

This Island Earth

The chains of potential health outcomes from changes to Earth's environment are tangled. Increases in carbon dioxide levels deplete crops' nutritional value, while heat, drought, salinity from encroaching seas, and ground-level ozone lower crop yields. Ocean acidification and warming lead to shortages of food from the sea and push hungry people to seek alternative protein sources, some of which can increase opportunities to contract zoonotic diseases. Food scarcity driven by insufficient supply and higher prices threatens health and presages conflicts. Inhospitable climate conditions drive human migrations, which compromise individual health and strain community resources, increase social tensions, and contribute to political and economic destabilization. The conditions of poverty complicate everything in innumerable ways.

And health threats don't necessarily stick to their region of origin. For the moment, the United States may be more insulated from climate consequences than other countries, says Murray, but infectious diseases and airborne dust and soot don't acknowledge international boundaries.

The trouble is, biomedical research isn't structured to tackle a problem of this magnitude and complexity, Murray adds.

"The way we do science is to isolate very specific testable questions, and that's not how ecology works," she says. "We're going to have to think about things creatively and holistically. It can be a big challenge to move from hypothesis testing and even 'big data' sort of stuff to narratives of what can happen and how things are connected."

Fear of losing funding or peers' respect also may deter biomedical investigators from probing climate questions. Whatever the reasons, the result has been an anemic literature that too often explores health consequences "in a very limited and uninteresting way," says Murray.

Doubling down on research could help specialists better predict the health ramifications of individual climate-driven events. An outbreak of West Nile virus surprised California in 2014, while the state was enduring its worst drought in 1,200 years. Researchers later determined that the parched land drove mosquitoes to swimming pools and other water sources near humans and extended the period during which egg-harboring females could transmit the virus.

When predictions are on target, lives are saved. Although more than 140 people had died by early September 2017 as floods inundated Bangladesh, government preparations ensured that for the first time, none of those deaths occurred from diarrheal diseases. Developing robust models that can calculate the likelihood of different health outcomes for a given scenario will be critical for understanding—and communicating—why "sometimes the same set of events will cause an epidemic and sometimes it won't," says Murray. As a side benefit, Murray points out, emphasizing probabilities rather than predicting doom with each climate-driven disaster could mitigate catastrophe fatigue among the public and reduce fodder for climate change deniers.

Tick, Tick, Tick

In January 2017, the *Bulletin of Atomic Scientists* advanced the Doomsday Clock—a symbol of human-caused apocalypse—by 30 seconds, in part because of climate change and its anticipated effects on human health. It's now two and a half minutes to midnight, the closest to doom since the atomic age ended.

Murray suspects that the "overwhelmingly scary" specter of irreversible and calamitous changes to Earth's environment frightens away many potential investigators.

"When the few scientists who are doing quality work in this area present at meetings, I think the rest of us kind of gasp and feel dizzy," she says. "It's so ominous. We don't know how to respond."

Rising to the research challenge, however, could uncover critical information and reveal new solutions that illuminate paths toward a less dire future.

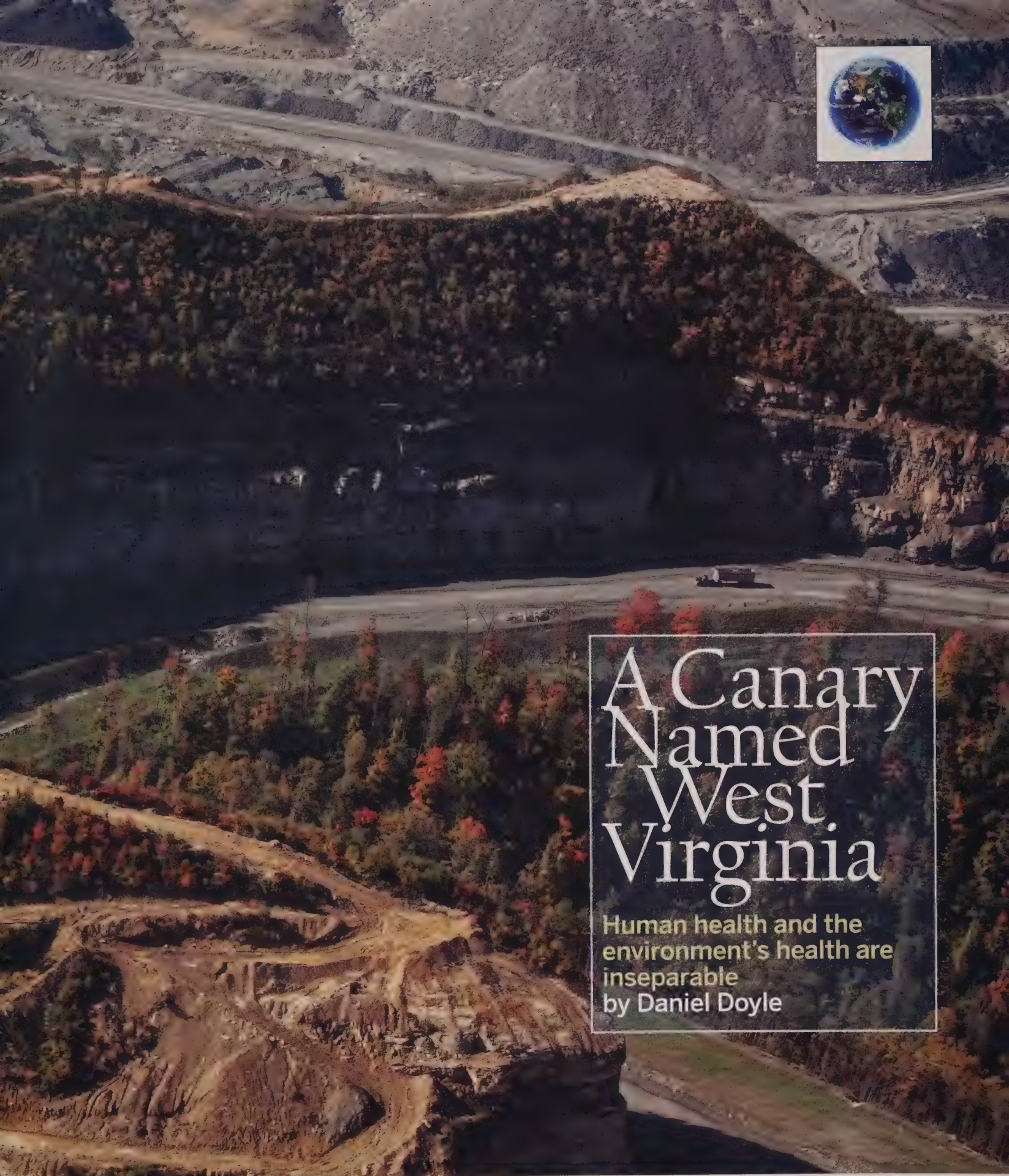
Murray places faith in human ingenuity, yet inadequate funding, large-scale barriers to implementation, and lagging participation by excellent researchers limit her hope. There's also the uncomfortable knowledge that research alone won't be enough.

"I can do some relevant science," says Klerman, "but I need somebody else in public health or politics who can then translate that science into something that will lessen the effects of climate change and other adverse conditions."

What will ultimately induce a critical mass of research and spur public policy remains to be realized.

"It's going to take some disaster before anybody does anything," says Murray. "My hope is that the disaster won't be so extreme that it's irreversible." ■

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.



A Canary Named West Virginia

Human health and the environment's health are inseparable

by Daniel Doyle

Daniel Doyle (center) walks with neighbor Sandra Keeney and two of her children, Morgan and Aaden.

andra Keeney grew up on Wolf Creek in Fayette County in southern West Virginia. She lives a mile out Wolf Creek Road from me.

"My grandparents, Betty and Hayward Backus, bought this farm right on the creek in 1962," Sandra says. "I was born in 1980 right here. We swam and played in the creek when I was growing up. We had a well next to the creek, where we got all our water. In 1984, my grandmother heard about the PCBs [polychlorinated biphenyls] at Minden and told us we should stop drinking the water."

Wolf Creek begins on Summerlee Mountain about five miles west of Sandra's home. The creek runs past the old Summerlee mine slate dump, where coal waste has been piled for years. In 1994, federal inspectors found metals and acid draining from the slate dump into the waters of Wolf Creek.

In 2016, Sandra learned that pollution from a new source was getting into the creek. The Danny Webb Construction Company of Lochgelly, West Virginia, was injecting fracking discharge, a water-chemical mixture produced in drilling for natural gas, into old gas wells along Wolf Creek. A study published that year by the U.S. Geological Survey in *Environmental Science and Technology* reported that strontium, barium, lithium, and radioactive compounds were leaking into the creek from the injection facility. A separate study that same year in *Science of the Total Environment* by researchers from Duke University found endocrine-disrupting compounds downstream from the injection site. Despite the company's repeated violations of state regulations, the West Virginia Department of Environmental Protection had not shut them down.

In January 2017, Sandra's children developed sores—blistered and red rashes—on their arms and face after bathing in water from the family's well. Sandra took the kids to their doctor. The sores, the doctor told her, were chemical burns.

There is a sandy bank along the creek that runs next to the family's fields. "This used to be our favorite playground," say Sandra's children. "But now mom says we can't play here anymore."

Insults and Injuries

Ten years earlier, in neighboring Boone County, near the state capital of Charleston, Jennifer Hall-Massey and her family had been having problems similar to those Sandra's family later experienced. As reported in the *New York Times*, the Hall-Massey family noticed that the water from their well had grown cloudy and foul smelling. Jennifer's children developed skin sores after bathing, and their teeth began to decay rapidly. Tests showed the presence of metals including arsenic, lead, barium, manganese, and nickel in their tap water. In 2009, the year the *Times* reported her story, Jennifer and nearly 300 of her neighbors sued nine coal companies, including the coal-mining giants Massey Energy and Patriot Coal, charging them with discharging dangerous waste into local water supplies. State records revealed that coal operations within eight miles of Hall-Massey's home had injected more than 1.9 billion gallons of coal slurry into the ground since 2004. The state's environmental protection department sided with the companies, claiming it could find no evidence of the pollution. The suit was settled in 2012 for an undisclosed amount.

In 2004 in nearby Mingo County, 700 residents from four communities sued Rawl Sales and Processing, a subsidiary of Massey Energy, for polluting their public water systems by pumping 1.4 billion gallons of toxic coal slurry into underground mines. The suit was settled for $35 million in 2011.

As wells and public water systems serving small communities closed because of disruption and pollution from surface mine blasting and coal slurry injection, more and more communities became connected to large corporate water systems, especially the system operated by West Virginia American Water Company in Charleston.

On January 9, 2014, 11,000 gallons of crude MCHM (4-methylcyclohexane methanol) and polyglycol ethers, agents that remove impurities from coal and thus increase its value, leaked from a 48,000-gallon aboveground tank owned by Freedom Industries into the Elk River, about one and a half miles above the intake for West Virginia American Water. Three hundred thousand people living in nine counties, an area that included the city of Charleston, were without safe drinking water for more than a week. Residents reported that tap water had a sweet, licorice odor. Hundreds of people were treated in local emergency departments for nausea, vomiting, and rashes. Nearly 700 called the West Virginia Poison Control line.

At community meetings and legislative hearings during that water crisis, residents and business owners expressed anger and frustration, repeating complaints heard since the 1980s that West Virginia had become a "national sacrifice zone"—an "extraction colony."

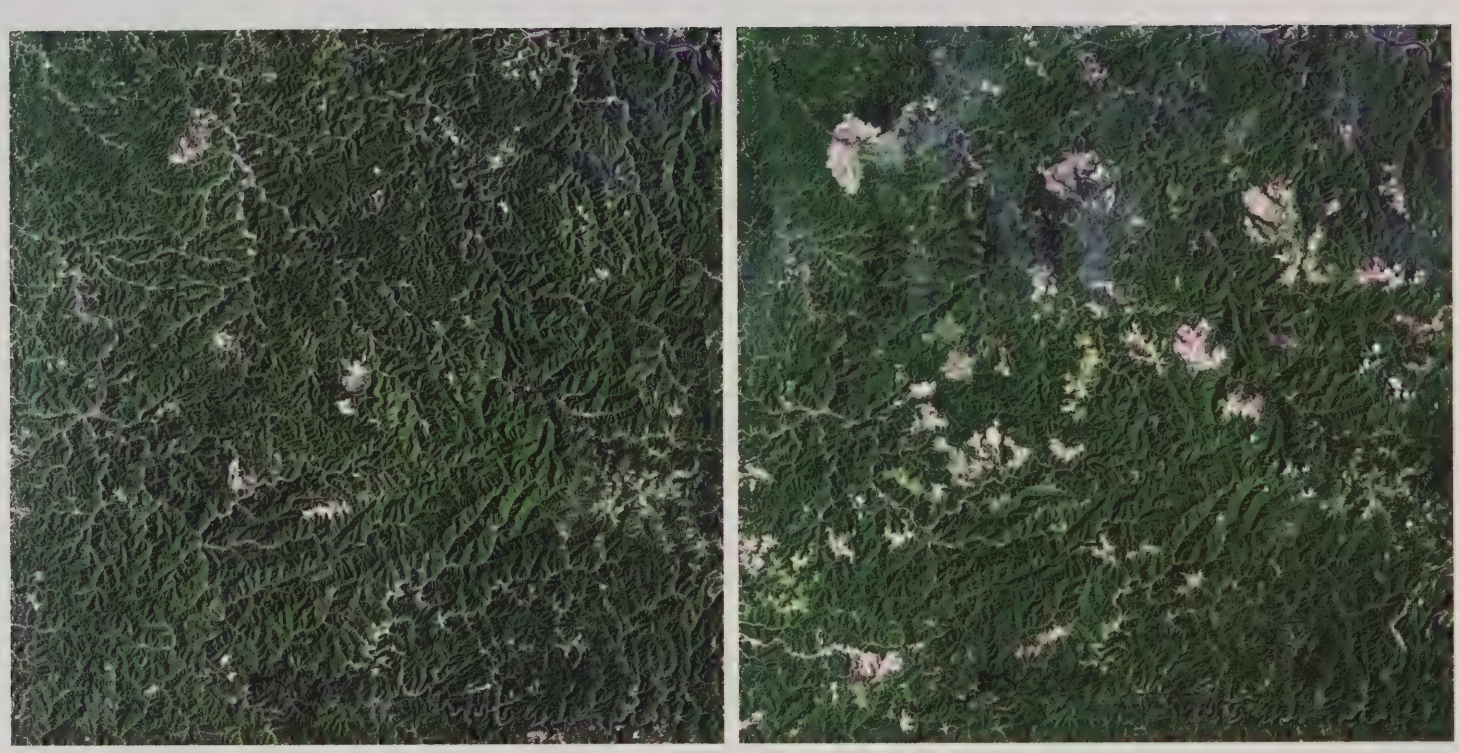
Open Wounds

Mountaintop removal (MTR) mining is a growing concern for people living in affected communities in West Virginia and Central Appalachia along with those in the environmental movement in this region.

A combination of state and federal actions, played out over decades, gave birth to the MTR industry of today. MTR is a form of strip mining, a type of surface mining that has been going on since the early 1960s. In the late 1970s there was a move to more tightly regulate strip mining nationally, but the resulting federal law contained a loophole that opened the way to MTR. In 1990, this loophole began to attract the attention of the mining industry. In that year, Congress amended the Clean Air Act to encourage utilities to burn lower sulfur coal, a form of coal abundant in southern West Virginia and easily accessed through surface mining. Around the same time the West Virginia state legislature, hoping to stimulate job creation, established so-called super tax credits for coal companies. The companies quickly took advantage of the credits to buy giant excavation machines and other surface-mining equipment.

Mountaintop removal mining took off.

Compared with underground mining, MTR is more cost effective as it requires fewer workers and gives access to coal seams normally too thin to mine. How it allows this access is part of the concern: it literally removes the tops of mountains. For miles and miles, mountaintops get cut off and the over-



Surface mining, including mountaintop removal, has been in use in West Virginia for decades. The images show the increase in surface-mining sites within a recent twenty-five year period (June 6, 1987, left; June 8, 2011, right). Scientific evidence indicates that the environmental disturbances this type of mining causes are pervasive and irreversible.

burden, the rock and soil that lie above the coal, is dumped into surrounding valleys.

The devastation and scale of MTR is unimaginable until you see it. Whole valleys are filled with overburden. Streams are buried and polluted in violation of the Clean Water Act. Illegal discharges of mine runoff are so common that personnel in the state's Department of Environmental Protection cannot keep up, even if their actions were not being blocked by coal-friendly government officials.

Stewards of the Land

West Virginians have been protesting the environmental and health impacts of mining and logging for more than a century.

An early advocate for the state's environment was native son Alonzo Beecher Brooks. In 1911, Brooks, a forester who lived at the turn of the twentieth century, wrote a 480-page report for the West Virginia Geologic Survey describing the importance of forest preservation and the harmful public health impacts of overlogging.

In the mid-1960s, the West Virginia Highlands Conservancy began to protect some of the most pristine areas of the state from ill-conceived highways, dams, logging, and mining projects. The group formed one of the first mining committees to oppose mountaintop removal. From those efforts grew the West Virginia Environmental Council, which formed in 1989. The E-Council, as it's known, has had many important legislative achievements over the past thirty years, including landmark legislation for groundwater protection.

In 1987, a group of Huntington, West Virginia, residents organized to oppose construction of a huge BASF Chemical Company hazardous waste incinerator on the Ohio River at nearby Ironton, Ohio. Calling themselves the Ohio Valley Environmental Coalition, they successfully stopped the incinerator project, an action that has helped protect the Ohio River and waters all the way to the Gulf of Mexico. In the three decades since that action, coalition members have led efforts to protect community health and the mountain environment by effectively exposing and opposing the public health hazards of MTR, deep oil and gas fracking, and related pipeline projects throughout West Virginia.

Appalachian Mountain Advocates, a group that began its work in 1998, has, according to its founder, Joe Lovett, "worked successfully to hold the coal industry accountable." That same year, Lovett, an environmental attorney, brought his first case challenging MTR. Since then, Lovett and his team of attorneys have brought a series of lawsuits against MTR mining operations on behalf of communities affected by this form of mining. Many of the lawsuits have resulted in landmark decisions. "It's my view," says Lovett, "that we need to move to renewable energy in this country."

In Fayette County, where I live, a group called Headwaters Defense formed in 2015 to do what the state's Department of Environmental Protection seems unwilling or unable to do: stop Danny Webb Construction from injecting fracking waste into old gas wells near Wolf Creek. Led by local residents Brandon Richardson, Brad Keenan, and Britt Huerta, Headwaters collected 5,000 signatures from county residents in 2015, prompting the Fayette County Commission to adopt an ordinance banning disposal of fracking waste in the county. The celebration was short, however, for natural gas giant EQT went to court to block enforcement of the ordinance. In late August, the U.S. Fourth Circuit Court of Appeals in Richmond, Virginia, decided in favor of EQT.

The group has also taken up the cause of Sandra's family and other Minden residents who live next to the Superfund site created by the dumping of PCBs from mine transformers in the 1970s and 1980s. In a recent interview for a Univision documentary on PCBs, Richardson said, "I fear that not only

will the people go extinct in Minden, but I fear that the history of PCB contamination in Minden will be swept under the rug. No one will know that this is a mass gravesite of a once bustling coal mine town filled with people who loved each other."

The Evidence, Please

Ten years ago, Michael Hendryx was new to the faculty of community medicine at West Virginia University. Although his specialty is epidemiology, as a newcomer to the state he had not known of the health effects that coal mining, especially MTR, has had on surrounding communities.

He soon learned.

During the next seven years, Hendryx and colleagues published more than eighteen peer-reviewed articles on the damaging health effects of MTR mining. Their research showed that in rural communities near MTR mining operations, residents have higher cancer rates (*Journal of Community Health*, 2012), more cardiovascular disease (*American Journal of Public Health*, 2008), and lower quality of life (*Public Health Reports*, 2009) than people who live in rural areas of the state that don't have mining operations. In addition, the researchers chronicled socioeconomic differences: Communities in the shadow of these mining operations also had degraded water quality (*Water Quality, Exposure and Health*, 2012) and higher rates of poverty (*Journal of Health Disparities Research and Practice*, 2010).

From a generational health-effects perspective, their most important study may be one that reported the association between MTR mining and birth defects. In that paper, which appeared in May 2011 in *Environmental Research*, Hendryx and colleagues reported a heightened prevalence of birth defects in MTR counties compared to nonmining counties of central Appalachia, after controlling for covariates such as cigarette smoking during pregnancy and socioeconomic disadvantage.

In July 2017, Hendryx testified before a National Academy of Sciences panel that there is sufficient evidence of public health harm to end the practice of MTR. *Charleston Gazette* reporter Ken Ward, who covered Hendryx's appearance, wrote "West Virginia political and governmental leaders have mostly either ignored the growing body of science on mountaintop removal's health effects or tried to belittle the work. Coal industry officials have, likewise, attacked the studies, funding a large effort to discredit the work."

Climate change is real and is caused by the burning of fossil fuels. There is no more time to waste: we must embrace sustainable forms of energy and change our own behaviors to ensure greater energy conservation and efficiency.

Ward's assessment was an understatement. One month after Hendryx's appearance, the U.S. Department of the Interior, acting under a directive from the White House, halted a large, long-term study by the National Academies of Sciences, Engineering and Medicine into the human health effects of surface mining such as MTR. The brake on funding, according to a department statement, is part of a budget review of all grants greater than $100,000.

Coal-Fueled Heat

The state-based environmental protection movement has been vocal, but the coal industry has been far from silent.

In 2008, the industry launched the Friends of Coal campaign. Funded by millions of dollars from the West Virginia Coal Association, the Kentucky Coal Association, the Virginia Mining Association, and the National Mining Association, the campaign is a multimedia effort to convince people in the state that environmental laws and regulations are unreasonable, unnecessary, damaging to the state's economy, and deadly to the jobs base. At car shows, football games, and community picnics and on yard signs, bumper stickers, and license plates, the message is that efforts to preserve and protect the environment represent a war on coal—and on West Virginia. The strategy is to conflate the proud tradition of sacrifice and hard work by coal-mining families with the single-minded corporate interests of maximizing short-term profits at any cost.

The Friends of Coal campaign and its "war on coal" message were particularly fierce during the Obama administration, when their attacks on the president and the U.S. Environmental Protection Agency were common. In a state that is pro-gun, socially conservative, and 94 percent white, it was often not hard for those arguments to gain traction.

State-based environmental groups have not given up, however. Faced with the Friends of Coal campaign and its messages, they have organized a Friends of Water campaign.

Truth to Power

For most of the twentieth century, coal was king in West Virginia. It put food on the table, clothes on the kids, and heat in the stove for millions of families. After unionization and World War II, coal mining provided a path to excellent health care, new cars, and college education, and coal-mining families became solidly middle class.

Although coal really did keep the lights on, the world is changing. Mining jobs are dwindling as automation and new processes cut the need for human workers and as natural gas production undercuts the demand for coal. But an even more important shift is our knowledge that climate change is real and is caused by the burning of fossil fuels. There is no more time to waste: we must embrace sustainable forms of energy and change our own behaviors to ensure greater energy conservation and efficiency.

In my own practice, I'm much more likely to consider occupational and environmental exposures to toxic substances as causes of disease than I was in earlier years. I share this perspective with students and colleagues whenever I can. I'm concerned that current medical school curricula still put too little emphasis on occupational and environmental causes of disease. I hope I am wrong.

I believe strongly that health advocacy is part of our job as physicians. Usually, that means helping our patients get what they need by filling out forms or fighting with insurance companies for precertification for medicines and procedures.

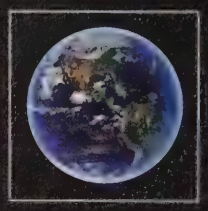
But sometimes it means standing up and speaking out against a threat to the health of our whole community, regardless of whether that community is our town, our state, or our planet. ■

Daniel Doyle '72 has practiced family medicine at New River Health Association in Fayette County since 1977. *The author wishes to thank Paul Corbit Brown, Sandra Keeney, Brandon Richardson, and Vivian Stockman for contributing to this article.*

AFTER EFFECTS

Scientists work to uncover how epigenetic mechanisms may influence genes and development

by Greta Friar



The chemical was everywhere: in water bottles and children's sippy cups, dental sealants, and the linings of food cans. It was detected in the urine of more than 90 percent of the people in this country and suspected of causing markedly decreased fertility rates in workers in the factories that made products containing the chemical. Animal studies added to the grim litany: the chemical disrupted endocrine hormones and may have caused health problems from cancer to heart disease to impotence and low fertility. ■ This pervasive chemical was bisphenol A, commonly known as BPA, a substance that the U.S. Food and Drug Administration considered safe, even as it opened an investigation into its effects on human health in 2008. In its 2014 update on the chemical, the agency still listed it as safe for humans when used in the levels found in food packaging.

Fred Winston

Yet many scientists, including some at HMS, have expressed skepticism over the generally recognized as safe designation. Animal studies, after all, had found not only that BPA was damaging to organisms exposed to it, but also that it could affect their offspring. In short, researchers said, the chemical's damage appeared to be inherited.

In the past decade, many scientists have attempted to further our understanding of how environmental exposures affect our long-term health. Doing so has proved difficult. Take BPA as an example. The chemical's presence in such a large percentage of the population makes designing rigorous, controlled studies a daunting task. Animal studies, therefore, take on a greater empirical role even as some people question whether findings in animals are useful representations of human health. Furthermore, in the research community, there is some disagreement over which biological mechanisms are affected by environmental influences and how these changes occur at a molecular level. Then there's the big question: How big a role does the environment play in human health risk?

Currently, a growing body of research that seeks to shed some light on these questions is delving into what is known as the epigenome, an intricate system of molecules that interact with an organism's DNA. It is one of many strategies employed by cells to control gene expression.

Traffic Control

While DNA is the complete instruction manual for building an organism and keeping it running, the epigenome is one of the several mechanisms used to control which of those instructions should be fol-

lowed and when. This orchestration aids in the formation of tissues and organs during development and the timely production of proteins during an organism's life.

Epigenetic changes do not affect genes directly, as genetic changes do. Instead, they operate on "top" of DNA, not within it, as mutations do, and cannot rewrite the information that a gene encodes. When the genome is replicated during cell division, epigenetic marks, the molecules that label genes to be switched on or off, are sometimes copied and preserved alongside the genes they control. In such cases, the changes become heritable.

Molecular Mechanics

Fred Winston, the John Emory Andrus Professor of Genetics at HMS, has spent decades studying genetics and epigenetics in yeast and has watched the field of epigenetics gain prominence. For some time, Winston says, there has been one acknowledged epigenetic mechanism: DNA methylation.

The work that helped identify that key mechanism dates to the mid-1970s, according to a 2014 report in *Cold Spring Harbor Perspectives in Biology* that discusses the field's history. Around that period, scientists began proposing that DNA methylation, a natural process in which specialized enzymes attach a methyl group to a gene, may act to prevent a gene from being transcribed, effectively turning it off.

This control process, it was found, could sometimes be influenced by chemicals from the environment, which themselves add methyl groups or, in some cases, act to remove methyl groups that keep a gene quiet. Because some of these epigenetic marks persist over an organism's life, DNA methylation is a mechanism proved to be heritable.

Another epigenetic mechanism described in that report is histone modification, which acts by altering the physical structure that houses DNA. In cells, DNA spools around histone proteins. Chemical groups, including methyl groups, can attach to the histones and either activate or repress transcription, depending upon the particular modification. Although scientists in the 1950s were already proposing that histones may act to repress gene expression, direct evidence of how molecular changes to histone affect gene expression was not documented until the 1990s.

As the field has matured, additional mechanisms for epigenetic changes have been described. In the HMS laboratory of Scott Kennedy, for example, work with *Caenorhabditis elegans*, a millimeter-long transparent nematode, has shown that epigenetic information can be inherited via a nuclear RNA interference (RNAi) pathway that uses noncoding RNA as informational vectors capable of transferring gene-silencing information over generations. In written material describing his work, Kennedy, the Philip and Aya Leder Professor of Genetics at HMS, notes that the findings from his team of investigators have led them to propose that animals may "use the nuclear RNAi machinery to transmit epigenetic information, accrued by past generations, into future generations to regulate important biological processes."

Such discoveries are promising for the field and for efforts to understand environmental effects on gene expression and development.

"There are a lot of epigenetic factors we've known about for a long time, but their real roles are still poorly understood," Winston says. "Now, as technology has advanced, we're able to study responses to environmental stresses in microorganisms under many different conditions. This is very exciting."

Early Action

Monica Colaiácovo is one HMS scientist who is trying to solve questions of how organisms respond to environmental stresses—questions that immerse her in work that is helping to describe epigenetic mechanisms and the heritability of epigenetic changes. When the FDA began looking into BPA's effects on humans, for instance, Colaiácovo was one of the many researchers across the country who became curious about the chemical's potential effects on humans. Colaiácovo, an HMS professor of genetics, studies reproduction in *C. elegans*, focusing on meiosis, the biological process that results in egg and sperm cells with genomes that vary from the parents' genome, so BPA's observed effects on human fertility and reproduction interested her. How, she wondered, might the chemical affect meiosis?

In her 2010 paper, Colaiácovo showed that BPA had grave effects on fertility and reproduction. It caused sterility, prevented the creation of genetically healthy egg cells, and increased the likelihood that embryos would die.

In her 2010 paper in the *Proceedings of the National Academies of Science*, Colaiácovo showed that BPA had grave effects on fertility and reproduction. It caused sterility, prevented the creation of genetically healthy egg cells, and increased the likelihood that embryos would die. The chemical, she realized, changed the expression of genes in *C. elegans*. The findings were so sobering that Colaiácovo became concerned over the health risks of environmental exposure to other chemicals that were considered safe by regulatory bodies like the FDA.

"So many chemicals are introduced into our environment every year," Colaiácovo says, "but we have little understanding of their effects on our health."

Although the human body has ways to eliminate toxic chemicals so that their immediate health effects are limited, studies suggest that some of the changes these chemicals may cause to the epigenome are maintained during cellular replication throughout an organism's life. Even a brief exposure to a harmful chemical, says Colaiácovo, may cause epigenetic changes that last long after any traces of that chemical have disappeared from the environment.

Environmentally induced changes in genome expression may be especially damaging during pregnancy and early childhood, and could fundamentally alter a developing infant, causing learning disabilities, brain abnormalities, and metabolic imbalances. Children are at higher risk for developing problems from such exposures, Colaiácovo says, because their bodies metabolize chemicals differently from how adults do in some cases, breaking them down more slowly, or in other cases not metabolizing them at all, allowing certain chemicals to linger longer and do more damage.

Furthermore, because the epigenome plays a critical role in prenatal development, its disruption can be ruinous to potential offspring. Cells use chemical signals to communicate and coordinate epigenetic regulation of organ development and tissue differentiation. Exposure to the wrong chemical signals, such as those introduced from the environment, can subvert embryonic development.

Monica Colaiácovo

Chirag Patel

The Big Picture

Determining which mechanisms drive epigenetic change and how they do so are not the only questions being investigated in the field. Researchers such as Chirag Patel, an HMS assistant professor of biomedical informatics, are working to find and replicate associations between environmental exposures and disease using human population data sets.

According to Patel, the tools epidemiological researchers can use to identify the environmental contributions to disease are less advanced than those available for determining a disease's genetic components, making it more difficult to pinpoint environmental links to disease. Despite this paucity, a growing body of research indicates that environmental factors may play a major role in many diseases, including cancers, diabetes, and heart disease.

There is a spirited debate over what defines an epigenetic change and the extent to which epigenetic changes are truly heritable from parent to offspring.

Investigating disease-environment associations requires Patel's research team to piece together data from national health surveys, health insurance data, and disease and pharmaceutical registries. The team's findings can be used by other researchers to prioritize experiments to determine whether an association is coincidental.

Correlations can be misleading, Patel says, so his research team uses several strategies to eliminate false associations and biases, including replication of findings in multiple sets of individuals; elucidation of the timeline of associations—did the chemical exposure appear first or did the disease—and encouraging other researchers to confirm findings with animal studies or laboratory analyses. Recently, his team has begun using twin studies to separate genetic and environmental causes.

Reproducibly associating chemical exposures with epigenetic changes and their health consequences requires population data that researchers typically don't have, says Patel. Epigenomic sequencing, which entails recording the methylation states and other epigenetic marks alongside both the genome sequence and environmental exposure information, is not common yet. Because of this, says Patel, there have not been nearly as many environment-wide association studies as genome-wide association studies.

"We've had some debatable evidence that some environmental exposures are correlated with changes in the epigenome," Patel says, "but I think what is missing in this field are methods to deduce causal connections."

Self-Correcting?

There is a spirited debate over what defines an epigenetic change and the extent to which epigenetic changes are truly heritable from parent to offspring.


Danesh Moazed

When epigenetic inheritance was first proposed, it reopened age-old debates about evolution. Before Charles Darwin put forward his theory of natural selection, another nineteenth-century scientist, Jean-Baptiste Lamarck, was advancing a different theory. Lamarck espoused the inheritance of acquired characteristics, in which organisms could pass to their offspring traits that the parents had acquired during their lifetime. Thus, according to Lamarck, if a giraffe, for example, kept reaching for the leaves highest on a tree, it would give birth to offspring with longer necks.

When genes were discovered, scientists saw that their function fit more closely with Darwin's theory. An organism's heritable traits resided in its genes and were determined before it was born. Later, when the epigenome and its role were discovered, scientists realized that the consequences of exposures during an organism's lifetime may be inherited by its offspring after all. The epigenetic mechanism was more limited in scope and not malleable by behavior as Lamarck envisioned, but it did challenge the modern understanding that genes were the sole carriers of inheritance.

Although many organisms, including nematodes, retain and pass along epigenetic marks from environmental exposure, human egg and sperm cells undergo extensive reprogramming during development. This reprogramming erases nearly all epigenetic marks.

The existence of this reprogramming function has made Danesh Moazed, an HMS professor of cell biology, skeptical of transgenerational epigenetic effects in humans. Moazed studies the regulation of gene expression in yeast and mammalian cells, including how epigenetic marks are maintained in yeast, an organism that has transgenerational epigenetic inheritance.

Moazed says that one of the important purposes of epigenetic reprogramming in human sperm and egg cells is to eliminate epigenetic changes that might be caused by the environment. The mechanism evolved, he says, to prevent environmental perturbations from being transmitted across generations. Mammals also seem to lack an RNA-based system that can transmit information from somatic cells to gametes seen in some invertebrates.

Moazed acknowledges that the chemicals pregnant women are exposed to can affect their offspring and that environmental factors can modify already-formed egg and sperm cells. But he does not think there is sufficient evidence showing true parent-to-offspring epigenetic inheritance in humans or most mammals. Instead, he says, effects in humans thought to be caused by transgenerational epigenetics are really examples of prenatal environmental exposure.

"Can epigenetics cause changes that could be stably transmitted for many, many generations?" Moazed asks. "Yes, in most extant life, but probably not in mammals."

The Long View

The extent to which chemicals in our environment can cause lasting, transgenerational epigenetic changes may be uncertain, Colaiácovo says, but she adds that whether transgenerational effects are a matter of true inheritance or simply of prenatal exposure, the health effects for future generations will be just as real. She points to the similarity between epigenetic mechanisms in nematodes and humans and to the consistency that exists between her lab's findings and observed effects in mice and humans. Colaiácovo thinks the outcome of her research in nematodes will illuminate the lasting health risks caused by the profusion of unregulated chemicals people are exposed to daily.

The possibility of such transgenerational effects is one of the issues that concerns Colaiácovo and drives part of her research.

Having shown that the effects of BPA during meiosis in nematodes were similar to those in mice and consistent with health problems observed in humans, Colaiácovo has now begun a screen of more than forty common environmental chemicals that are not currently designated as posing reproductive health risks by the FDA. The screen includes pesticides, chemicals used in fracking and crude oil processing, and phthalates, chemicals used in many different kinds of products including some plastics. Colaiácovo is exposing nematodes to these chemicals in dosages consistent with levels of human exposure. She's not sure what the screen will find, but the health implications could be substantial, especially for any chemicals that show transgenerational effects, given that some of those influences may be the result of epigenetic effects.

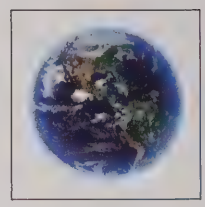
"My research into the effects of environmental exposure to chemicals began because of my interest in understanding the biology," Colaiácovo says, "but as my sisters and I started having children, the work has evolved into something that matters even more. I want to understand what could affect them and my future grandchildren."

"What are the chemicals that should be more tightly regulated?" she asks. "Are there better alternatives?

If we have the science, we can make these decisions and improve our reality." ■

Greta Friar is a Boston-based science writer.

NASA EARTH OBSERVATORY IMAGE BY JOSHUA STEVENS, USING MODIS DATA FROM LANCE/EOSDIS RAPID RESPONSE



FORCES ON NATURE

A different perspective on earthly events sobers and stuns

by Ann Marie Menting

◀ Wildfires in California, 2017

In October, northern California was consumed by fast-moving, intense wildfires that started in a few hundred acres in Napa Valley and, encouraged by powerful winds, triggered blazes in fourteen separate locations. By mid-month, the fires had burned nearly 300 square miles, caused thousands to evacuate, incinerated nearly 6,000 homes and businesses, and killed more than forty people.

According to area firefighters, the blaze in the northern region was fed by vegetation dried from nearly a decade of drought and fanned by dry winds traveling at velocities intensified by seasonal weather systems. Losses were heightened, firefighters added, because many of the fires followed historical fire corridors that are now filled with high-density housing developments.

Research by scientists in California finds that severe wildfires introduce nearly 18 percent of the particulate matter into the air over the United States and also increase the levels of pollutants—carbon monoxide, nitrogen oxides, ozone, and volatile organic compounds—that harm human health.

The psychological stresses from evacuation, uncertainty, and loss felt by California residents were exacerbated by the physiological stresses from the atmospheric pollution generated by the fires. During this period, San Francisco registered a particulate matter pollution level in the hazardous range: 404 out of a possible 500. The level is the highest since record keeping began in that city in 1999.

The air quality index is determined by the U.S. Environmental Protection Agency. When the index value is above 101, the air is considered to be unhealthy, with everyone at risk for adverse health effects. More vulnerable members of the population are at earliest risk; that is, members of groups designated as sensitive—older adults, children, and people with heart or lung disease. The index's scale is based on the degree to which five major air pollutants, regulated by the Clean Air Act, are present: ground-level ozone, particulate matter, carbon monoxide, sulfur dioxide, and nitrogen dioxide.

According to the EPA, ground-level ozone and airborne particulate matter are the two pollutants that pose the greatest risk to human health in this country.

▲ Alaska's Columbia Glacier

When British explorers surveyed the Columbia Glacier in 1794, its leading edge nosed the northernmost coast of Heather Island, a feature still seen in the bottom center of the July 1986 image above. The 2014 image (top, far right), from the NASA Earth Observatory, shows that this edge of the glacier has now retreated far up Columbia Bay. The reason: the glacier's ice has thinned to such a degree that tides in Columbia Bay disrupt its forward progress over water.

A 2016 report from the U.S. Global Change Research Program says that the losses of Arctic sea ice, the Greenland Ice Sheet, and Alaskan mountain and coastal sea ice will continue because of human activities driving changes in the planet's climate. Residents of Alaska, the report says, are among the first to experience the effects of decreased snow cover and loss of sea ice.

The reduced snow cover means less protection for the permafrost, further accelerating its erosion and its release of long-trapped carbon dioxide and methane, two gases that themselves contribute to atmospheric warming.

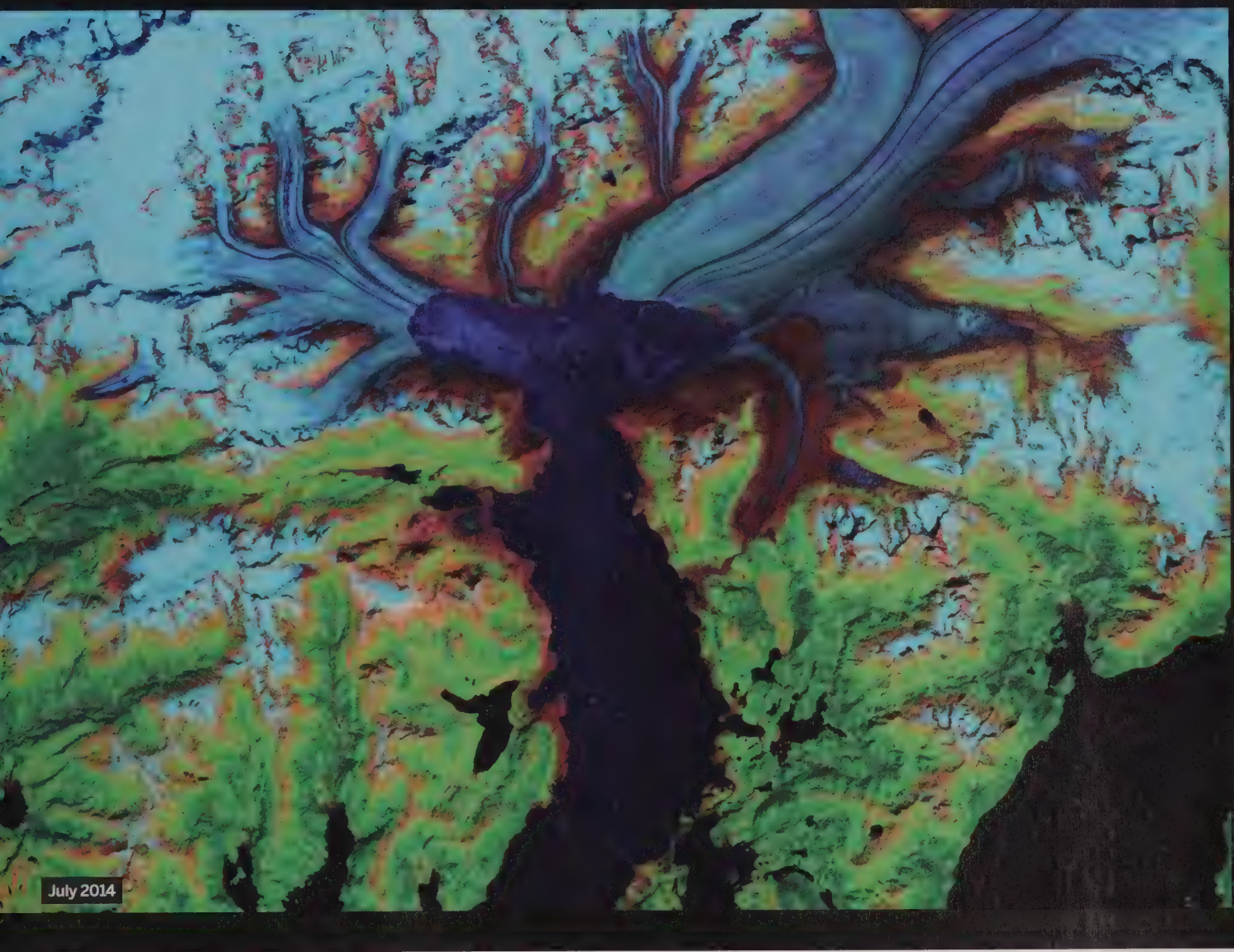
The increasing speed of ice melt, both sea ice and the frozen mass that makes up the Greenland sheet, is raising sea levels, jeopardizing coastal communities in Alaska and elsewhere, and eroding shorelines. Tidal flooding in U.S. coastal cities, a phenomenon worsened by rising sea levels, has increased as much as tenfold since the 1960s, and scientists are highly confident that this increase will continue.

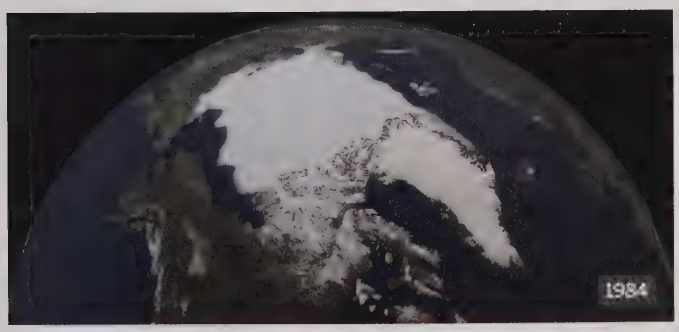
Melt from glaciers also alters the oceans' environment: the fresh water from glaciers depresses the heavier salt water and changes the oceans' temperature and salinity, which, in turn, affect currents. Increased ocean temperatures encourage blooms of various marine algae, many of which are harmful, even poisonous, to humans,

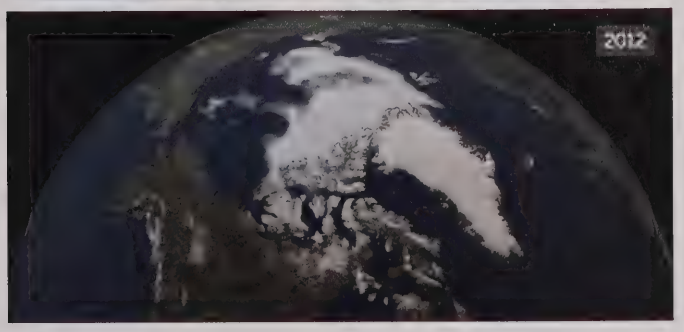
Because the oceans are the largest carbon sinks on the planet, the increase in anthropogenic carbon dioxide in the atmosphere is, according to research published in 2016, causing the oceans to become more acidic.

A 2017 report in *Nature* says scientists predict the oceans will move from their normal 8.1 pH to a more acidic 7.7 by 2100. This change, the report continues, has several ramifications, perhaps most visibly the destruction and death of coral and coral reefs, the loss of habitat for fish and other sea life that inhabit reefs, and disruption of the triggers necessary for shellfish reproduction.

Damage to sea life affects the chain of life in the oceans and, consequently, threatens a source of food and livelihood for millions of people.







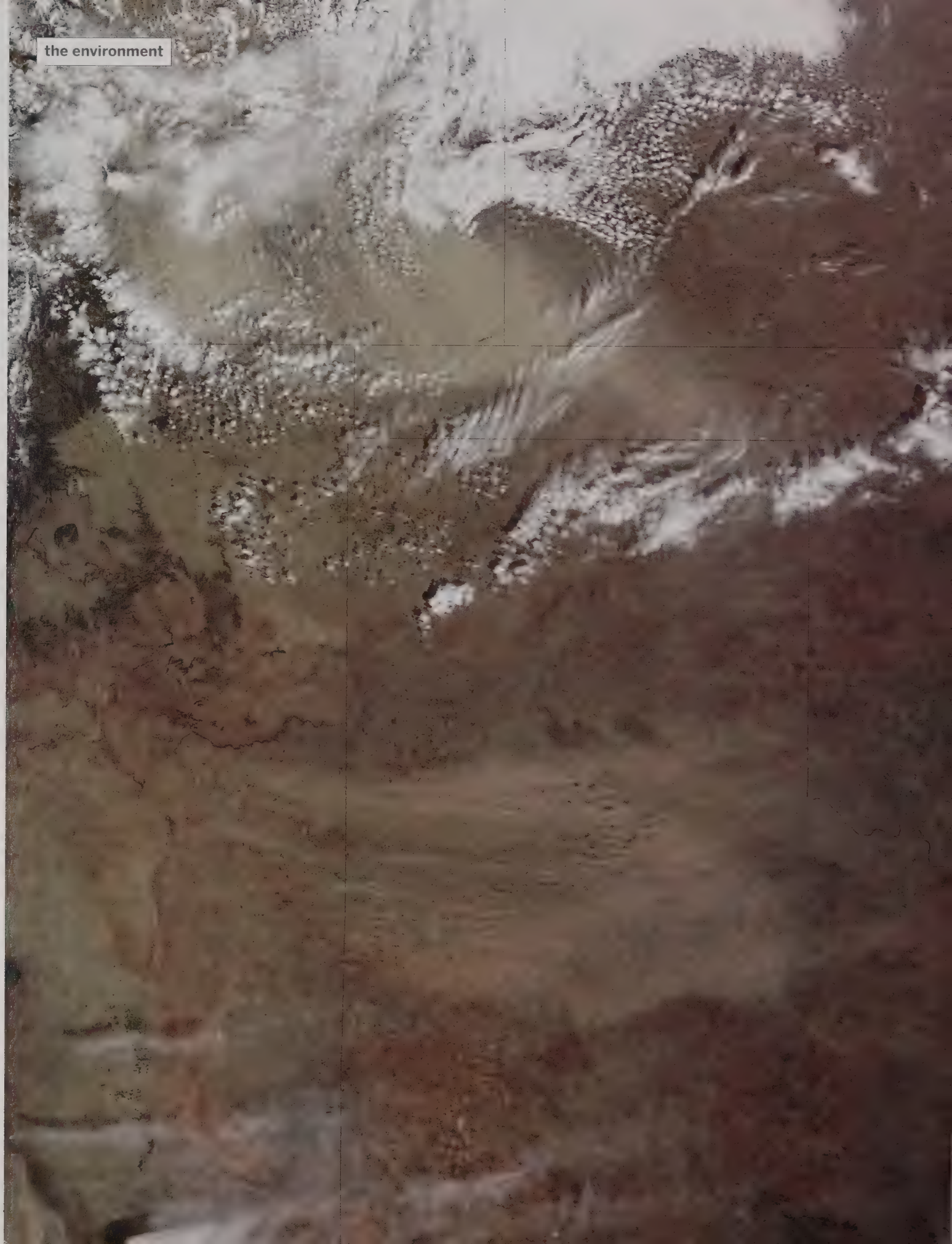
◀ Arctic sea ice

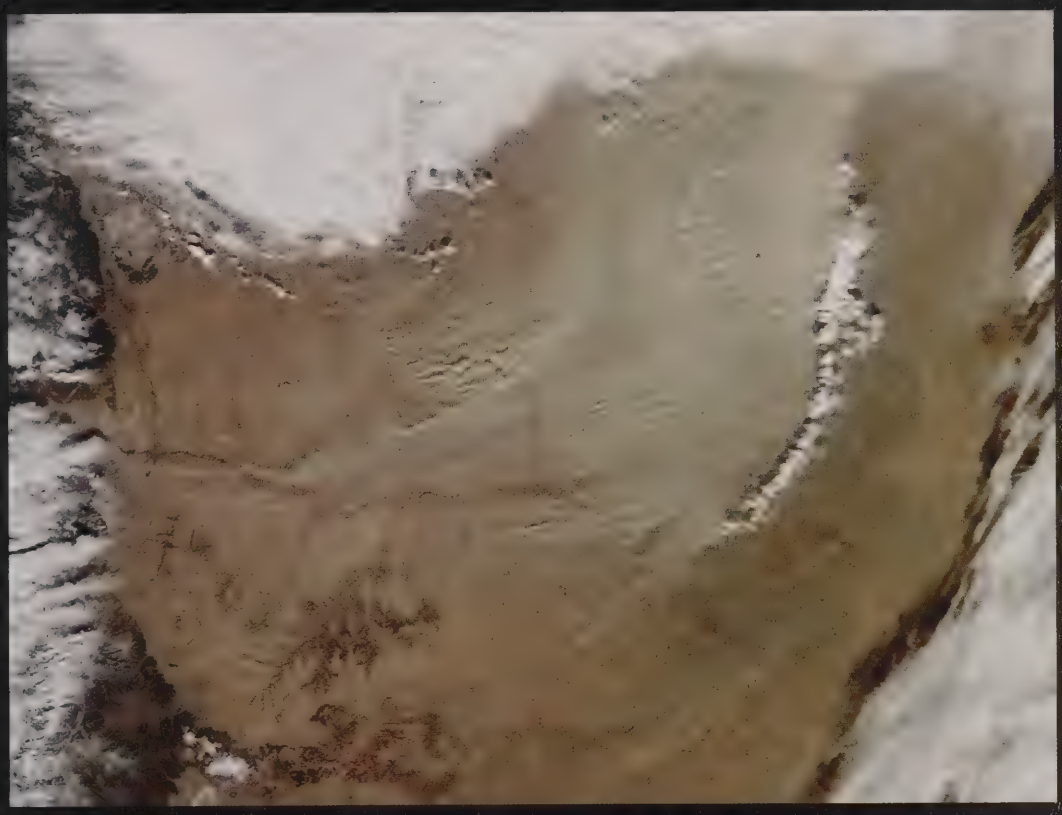
For decades, experts at NASA have been monitoring sea ice in the Arctic region and noting its behavior over time. Normally, the expanse of ice increases in winter and shrinks in summer, achieving its smallest footprint in September of any given year.

The 1984 satellite photo shows what was an average for minimum ice coverage between 1979 and 2000. The 2012 image shows a minimum coverage of about half the 1979-2000 coverage, a new low for minimum coverage. Despite a slight uptick in 2013, a downward trend of about 12 percent sea-ice loss per decade has occurred since the late 1970s.

This record of decline, according to the global change report, means that scientists can predict with very high confidence that the Arctic's summer ice will completely disappear within this century. In addition, they have equal certainty that observed sea- and land-ice losses in the Arctic region are outpacing climate model predictions.

Other Arctic scientists observe that the loss of glacier ice also removes large regions that reflect the sun's rays and help temper Earth's current climate.





◀ Dust storms in Texas, 2014

Twice in one week in March, large dust storms swallowed parts of Colorado, Kansas, New Mexico, Oklahoma, and Texas. Mid-month reports on the U.S. Drought Monitor describe soil moisture in western and central Texas and western Oklahoma as "virtually non-existent," the result of three months of rainfall that was only 10 percent of normal amounts. Strong winds worsened the drought's effects by wicking away surface moisture.

Of all the solid and liquid aerosols in our atmosphere, dust is one of the most abundant. It is generated or increased by factors linked with human activity, including agriculture, drought, and deforestation, as well as by soils lifted from naturally occurring deserts. Particulates in the air include sulfates, organic carbon, nitrates, mineral dust, and sea salt, which often clump together.

According to NASA scientists, 90 percent of aerosols have natural origins; that is, they arise from volcanic emissions, mineral dust, plants, algae, sea spray, and forest fires. Ten percent are anthropogenic, produced from activities such as fossil fuel combustion; emissions from power plants and other industrial sources; deforestation, overgrazing, drought, excessive irrigation, or other changes to the land; and domestic sources such as cigarettes, trash burning, and wood-burning stoves. Although human-caused levels are lower than those generated naturally, aerosols from human activity can concentrate in urban and industrial areas, heightening the risk to human health.

◀ Dust storms in Colorado and Kansas, 2013

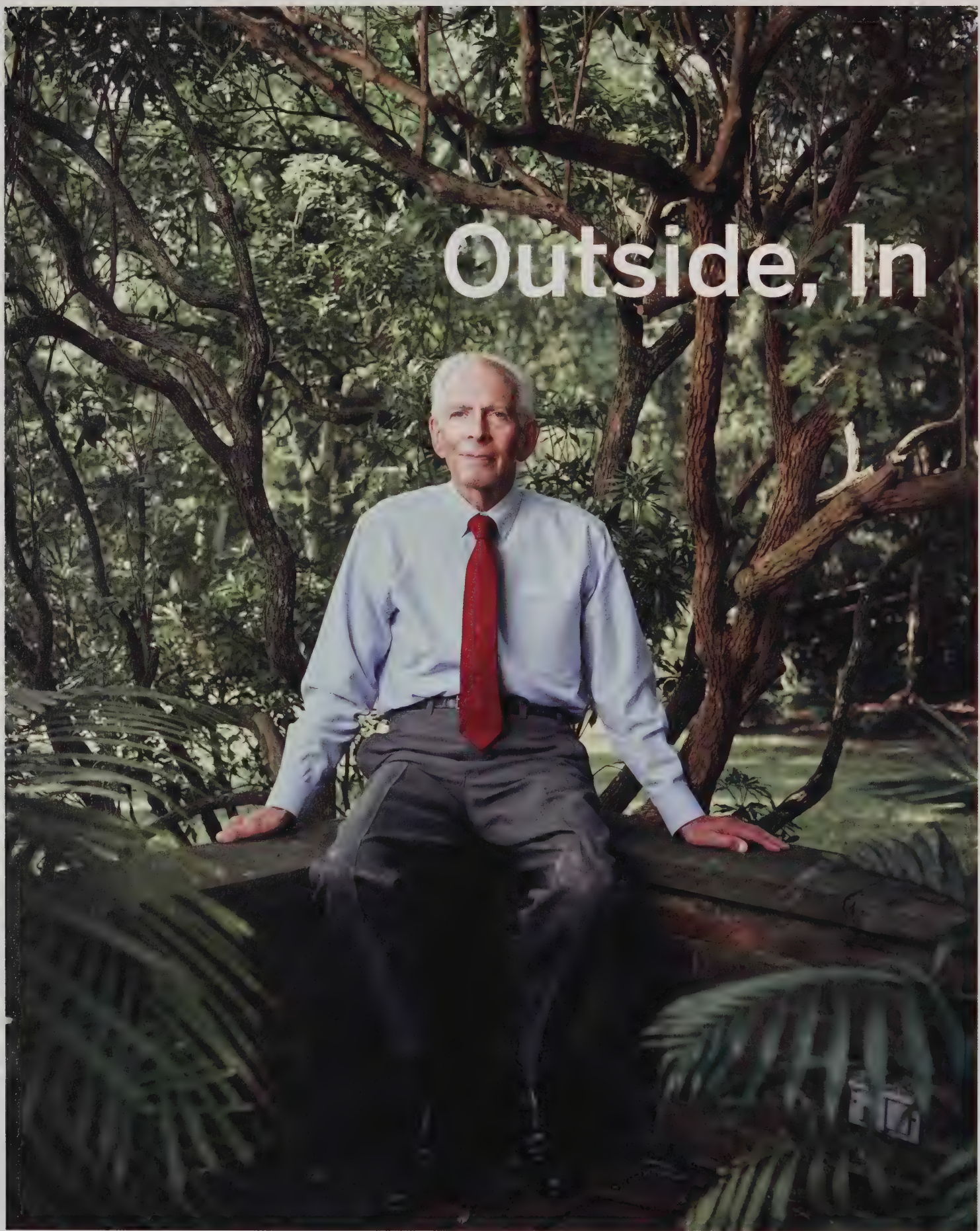
Exceptional drought conditions in early 2013 parched the land in western Kansas and southeastern Colorado, so when a cold front moved east, it swept up dry soil and gathered it into plumes of dust that were so thick, they reduced ground-level visibility to a quarter of a mile. One edge of the storm stretched 150 miles.

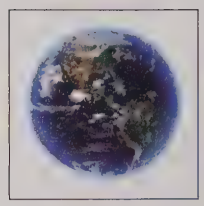
Dust storms are described as strong, turbulent winds that bear dust, soil, and sand across normally arid regions, such as the Great Plains region of this country.

According to a 2010 scientific report, the U.S. National Weather Service registers dust storms by drawing on various on-the-ground sources. But the report noted that there are no consistent criteria used by the reporting sources. Efforts to classify these storms, undertaken by groups such as the U.S. Department of Defense, have largely failed; scientists continue to explore new imaging tools that may allow accurate measures of airborne particles in dust storms.

Classifications may be uncertain, but the effects of these storms on human health are not. Dust storms saturate the air with particulate matter, which can harm respiratory and cardiovascular systems. They endanger drivers by hindering visibility and, by introducing disease-causing microorganisms such as fungi and bacteria into lungs and eyes, trigger a number of adverse health conditions including asthma, pneumonia, and stroke.

Outside, In





Physician-scientists track the profound effects the environment has on humans

by Susan Karcz and Ann Marie Menting

LLOYD TEPPER '57
Adjunct Professor of Occupational and Environmental Medicine
Perelman School of Medicine
University of Pennsylvania

THE PROBLEM Since his retirement as corporate medical director for Air Products & Chemicals two decades ago, Tepper has focused on teaching industrial toxicology to residents in occupational and environmental medicine at the Perelman School of Medicine at the University of Pennsylvania.

It can be hard, he says, to instill an appreciation of the effects that environmental toxins can have on patients. "'I don't have toxicology in my practice,' residents might tell me, or 'My work involves the ergonomics or medical criteria required for employment as a commercial driver or pilot,'" says Tepper. "So I take a moment to point out to them that the primary purpose of board certification is to protect the public. I tell them that if they claim to be board-certified in occupational medicine and an expert in the specialty, they are obligated to have a comprehensive grasp of the entire field, including the roles that toxic substances can have at the workplace and in the general environment."

THE WORK Lots of data exist on the risks that certain exogenous substances may pose to health and the environment. We must make wise use of that data, says Tepper. Analytical instrumentation and methods for detecting deviations from published reference "normals" in biological systems have dramatically improved, but, he notes, we need to better determine the endpoints that define harm.

"We have an obligation to determine which data are significant to human health," Tepper says. "We must ask what the data mean, and interpret them in a way that creates knowledge that goes beyond the numbers. We truly need knowledge—data in action."

HMS INFLUENCE As an undergraduate, Tepper wrestled with his choice of vocation: chemical engineering or medicine. He chose medicine, but has retained unfulfilled aspirations for chemical engineering.

During his senior year at HMS, he attended a lecture on occupational medicine given by Harriet Hardy, a pioneer in occupational medicine at Massachusetts General Hospital and the first woman appointed full professor at HMS.

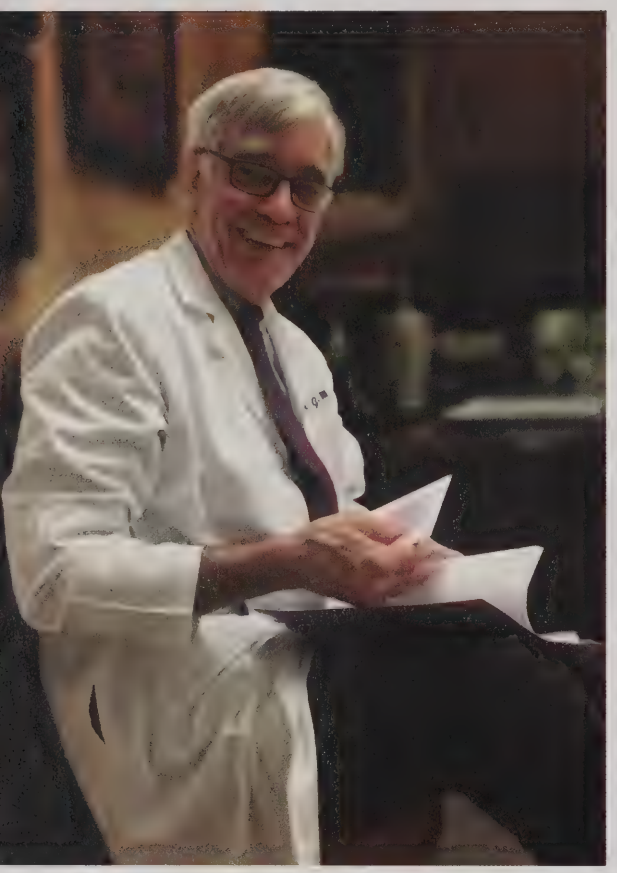
Her lecture, part of the School's preventive medicine curriculum, spoke to both of Tepper's interests. He participated in a four-year fellowship with Hardy that consisted of medicine at Mass General, industrial hygiene and radiological health at MIT, and a residency at what was then the Harvard School of Public Health.

The fellowship launched him into a career in occupational and environmental medicine, including work at the Atomic Energy Commission and as an associate commissioner for science at the U.S. Food and Drug Administration.

NEXT UP Tepper plans to continue his long-term relationship with the residency program at Penn and his work with the Society for Industrial Archeology, an organization that promotes the study, interpretation, and preservation of the physical artifacts of industry and technology.

As "the doctor" in that group, Tepper shares his knowledge of occupation-related illnesses among workers in extant and obsolete professions, from silicosis in flint knappers to mercurialism among smeltermen in California.

INFLUENTIAL BOOK *De Re Metallica* by Georgius Agricola, published in 1556 and translated (Latin to English) in 1912 by Herbert Hoover, before he became U.S. president, and his wife, Lou Henry Hoover



WILLIAM H. GOODSON III '71
Senior scientist and breast cancer surgeon and researcher
California Pacific Medical Center Research Institute

THE PROBLEM All of us, regardless of our health behaviors, are exposed daily to hundreds of environmental chemicals. Scientists are taking a new tack in cancer research, citing evidence that the current paradigm of exposure to a single "complete" carcinogen may miss the effects of cumulative exposure to mixtures of chemicals that work together to become carcinogens.

The increase in the age-adjusted incidence of breast cancer in the United States provides an example. Since the 1930s, the incidence has increased steadily and is now at about 129 cases in 100,000 women. Half of this increase was reported before mammography was in use. The incidence of breast cancer in men, however, while accounting for a much lower number of cases, follows a similar curve and is now about 25 percent higher than in the 1970s and double what it was in the 1930s. Goodson asks, "What in the world do men and women have in common?" His answer, "They all breathe the same air, drink the same water, eat the same food, and use similar cosmetic products."

THE WORK Goodson and colleagues have studied four common chemicals: BPA (bisphenol A; in can linings), PFOA (perfluorooctanoic acid; in Teflon), terephthalic acid (in #1 plastic), and methylparaben (in cosmetics). Each has different effects on cell growth and cell death and on markers of DNA damage, and each is a substance people come into contact with every day.

The Halifax Project, a global collaboration of researchers that includes Goodson and David Carpenter '63, has investigated eighty-five widely used "biologically disruptive chemicals," most of which the National Health and Nutrition Examination Survey (NHANES) has found in blood and urine samples from random people in the United States. The Halifax Project showed that cancer-related mechanisms were disrupted by low-dose chronic exposure to fifty of these chemicals, none of which is considered a classic carcinogen.

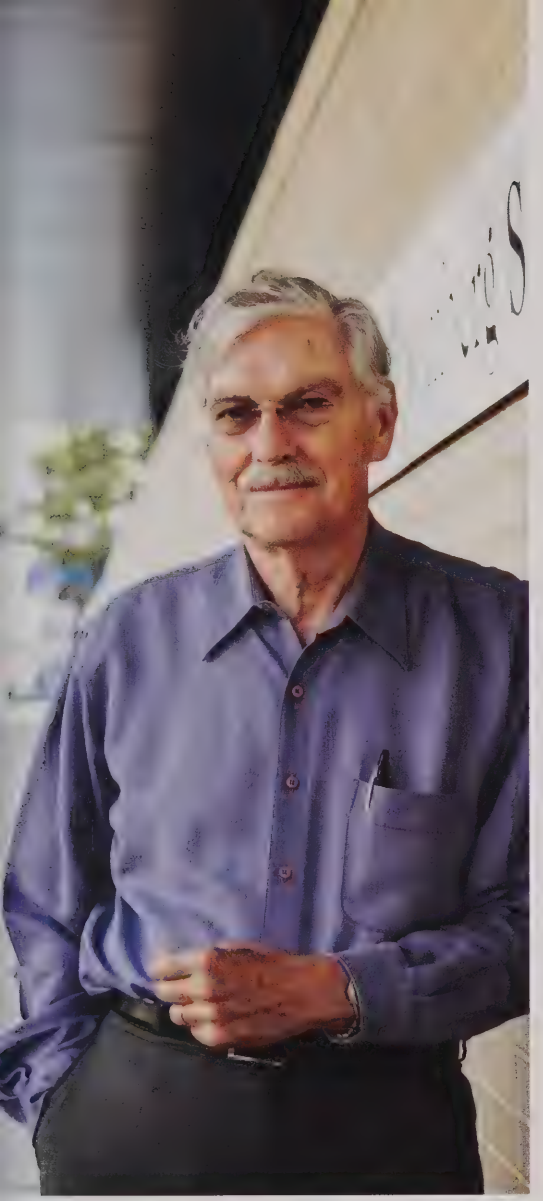
HMS INFLUENCE Goodson recalls that "HMS made it possible for students to spend a lot of time together, not just in classes." He found that the chance encounters, the casual conversations, were invaluable and allowed him to learn not only from the faculty but also from his peers.

William Silen, the HMS Johnson and Johnson Professor of Surgery Emeritus, and chief of surgery at Beth Israel Hospital at the time of Goodson's training, was a big influence. Silen used to tell trainees that a surgeon had to be as good an internist as an internist, and that surgery was just one more tool. "He had a great innate curiosity to understand what was going on instead of just operating on it," says Goodson.

NEXT UP Goodson sees two major challenges ahead. Because these exposures are ubiquitous, one challenge is how to conduct epidemiologic studies: everybody is already a subject and there can be no controls for comparison. The other challenge centers on how best to carry out this research in animal models. Questions to be answered include what makes cells grow? What makes cells not die?

INFLUENTIAL BOOKS *Silent Spring* by Rachel Carson and *The Great Lead Water Pipe Disaster* by Werner Troesken

Getting past the climate-change deniers involves delivering clear messages about how the environmental effects of a high-meat diet relate to an individual's health and the health of their family, where they live, and the planet.



JOHN SOARES

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Professor Emeritus of Medicine
Johns Hopkins School of Medicine

THE PROBLEM There are farms, and then there are factory farms. Agribusiness is a large part of the U.S. economy, one with recognized environmental and public health consequences. Antibiotic resistance, groundwater contamination, soil degradation, air pollution, loss of biodiversity, greenhouse gas emissions, and harmful levels of arsenic and nitrate in food and soil—all of these have been found to result from "big farma" operations.

THE RESEARCH The role that low-dose antibiotics used in industrial food-animal production play in the development of antibiotic resistance in humans has been well documented, yet these growth-promoting drugs are still used in the U.S. animal production industry.

Organic arsenic in poultry feed is broken down in the animal's gut into inorganic arsenic, a class-one carcinogen, which finds its way into chicken and turkey meat sold for human consumption. Colleagues in the Center for a Livable Future, founded by Lawrence in 1996, uncovered "smoking-gun evidence based on direct data collection and work with the poultry industry." Those findings led to the withdrawal of approval from the FDA for the remaining arsenical drugs in use in poultry feed.

Half of the seafood consumed globally now comes from farming, or aquaculture, which traditionally has relied on wild fish, an unsustainable source, as feed. Aquaculture is shifting to agriculture as a food source for farmed fish, thus linking the two food systems and potentially introducing further environmental stresses on already-taxed terrestrial farming and changing the nutritional composition of fish.

HMS INFLUENCE Lawrence's early work in primary/preventive care and health promotion launched him into a career in public health, including as a co-founder of Physicians for Human Rights. From his role as chief of medicine at Cambridge City Hospital (now Cambridge Health Alliance), where he witnessed the beginnings of the obesity epidemic in this country, to his role in establishing the Division of Primary Care at HMS, Lawrence has acted on his belief that health is a human right.

At Johns Hopkins Bloomberg School of Public Health, Lawrence's academic home since 1995, he was the associate dean for professional practice for a decade before focusing full time on the work of the center. The center's objective to not be "a think tank only, but a do tank as well" feeds its mission to translate science into policy and advocacy and to support research into solutions to problems in our food systems.

NEXT UP Advocacy and policy work have been Lawrence's arena for some time now, but it's still the next big thing. The challenge he sees in translating science for the general public and getting past the climate-change deniers involves delivering clear messages about how the environmental effects of a high-meat diet relate to an individual's health and the health of their family, where they live, and the planet.

INFLUENTIAL BOOK *A Sand County Almanac* by Aldo Leopold

ELIZABETH PEARCE HMS '97
Associate Professor of Medicine
Boston University School of Medicine

THE PROBLEM The only known use for iodine in the human body is to make thyroid hormone, the key regulator of metabolism. Although the U.S. population has been iodine sufficient since the 1940s, largely the result of the addition of iodine to salt, in recent decades evidence of lower iodine intakes are appearing in some populations, notably pregnant women.

This change is owed in part to a decrease in the consumption of iodized salt in this country. Adding to the problem of iodine insufficiency is the environmental ubiquity of perchlorate, a naturally occurring and synthetic chemical that competitively inhibits iodine uptake by the thyroid. In pregnant and lactating women, perchlorate exposure may reduce the level of thyroid hormone available to support the development of the fetus and newborn.

THE RESEARCH The U.S. population gets most of its dietary sodium from processed foods, which rarely contain iodized salt. Milk and dairy products provide most of our dietary iodine, meaning that vegans and people with lactose intolerance could be deficient. Dairy cattle take in iodine through their feed and from solutions used to clean the cows' teats. As Pearce puts it, "If dairy farmers decided

tomorrow to change the way they clean cows, we could all become iodine deficient."

To mitigate the health effects of perchlorate, Pearce, her colleagues, and others in the field are actively promoting the use of iodine-containing multivitamins for pregnant woman, women who are planning a pregnancy, and women who are breastfeeding. Pearce's research found that iodine is present in only about half of prenatal vitamins sold in this country.

Iodine is not mandated in the U.S. food supply. Although it's a cheap nutrient to add to foods, the effort to add it is not often made.

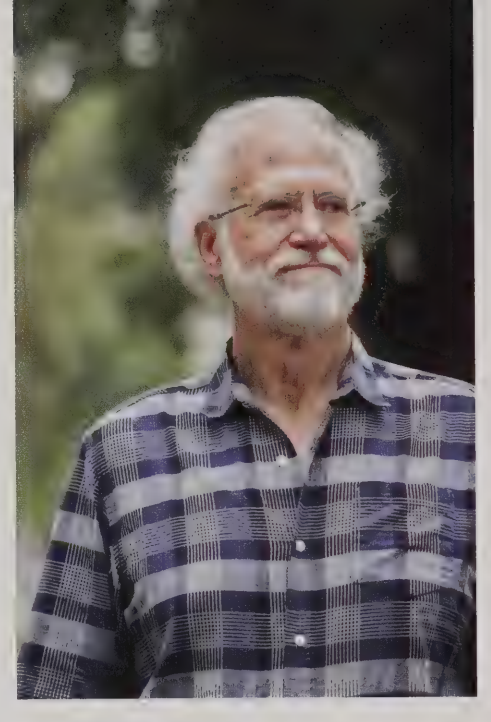
HMS INFLUENCE Although Pearce's interest in iodine nutrition emerged early in her career, it was her first endocrine rotation at Mass General under Gilbert Daniels '66, an HMS professor of medicine and director of the thyroid clinic at the hospital, that sparked her interest in all things thyroid. Her training as a thyroidologist took this interest further, leading to a passion for the public health effects of iodine nutrition and environmental disruptors of thyroid function, particularly in pregnant and lactating women.

Her parents count among Pearce's strongest influences, however. Her father, Dennis Niewoehner '65, is a pulmonologist, and her mother, Catherine, is an endocrinologist with a master's degree and an undergraduate degree from Harvard.

NEXT UP Research on the health effects of thyroid disruptors such as perchlorate is a relatively new field, and one that now has tools available for finer measurements and data collection.

In addition to determining what a safe level of perchlorate exposure is in pregnancy, Pearce aims to do more research on the long-term developmental effects of iodine deficiency and thyroidal disruptors on child development.

Findings from a study Pearce and colleagues published in *Environmental Research* earlier this year begin to delve into this area of interest. The researchers looked at the effects of perchlorate exposure on birth outcomes in a population of just under 2,000 mother-infant pairs in San Diego. The women were pregnant during a period between 2000 and 2003 when the county's water supply had been contaminated with perchlorate. The study results showed an association between this exposure and increased birthweight in male infants.



JOHN SOARES

DAVID WEGMAN '66

Professor Emeritus
Department of Work Environment
University of Massachusetts, Lowell

THE PROBLEM "How do you make decisions in the face of scientific uncertainty?" asks Wegman, "because you can't just wait to take action until everything is known." Some of the more contentious debates in environmental health today stem from the fact that changes proposed to enhance protection of health necessarily unsettles the status quo. Advocates for change will say there is enough evidence while those who have to make the changes, Wegman points out, will say the problem needs more study.

Wegman thinks occupational and environmental health conditions are more substantial determinants of the onset or course of disease than is generally recognized. Whether it's irregular work schedules that result in poor diabetes management or stress-filled working conditions that influence the development of cardiovascular disease, the science and medical communities, he says, must factor in the sometimes even far-upstream effects that environment can have on health.

THE WORK Wegman and others are conducting ongoing research in El Salvador among sugar cane workers. This workforce manifests a high incidence of kidney disease without evidence of hypertension or diabetes. Wegman's studies indicate that a simple intervention that provides easy access to water along with shade and rest is promising. The toll that heat takes on the workers, marked by their development of kidney disease, remains a challenge when physical demands and heat exposure are severe. Although mechanization would eliminate the problem, it would also result in workers losing jobs, with few employment alternatives available. Wegman expects similar tensions to arise in research to assess this type of kidney disease among migrant laborers in Texas and California.

In addition to gathering evidence of harm to workers, Wegman teaches public health students how to use incomplete evidence to help make policy.

"More important than anything else," says Wegman, "is to have the students understand that there is no absolute knowledge, and that you must be open to uncertainty even though it's going to be hard as heck to challenge your own paradigms."

HMS INFLUENCE Wegman's interest in public health is deep and wide. His father served as Secretary General of the Pan American Health Organization and as dean of the School of Public Health at the University of Michigan. But it was at Harvard that the spark for a career in preventive medicine was struck. David Rutstein '34, the Ridley Watts Professor of Preventive Medicine Emeritus at HMS, and Victor Sidel '57, a former member of the biophysics department at HMS and a past president and emeritus board member of Physicians for Social Responsibility, are two of Wegman's early influences.

"My first publication," says Wegman, "was a study Steve Schoenbaum '66 and I did while students. We investigated the delivery of health care in Cambridgeport. It was a project that grew from an assignment from Rutstein—how is medical care delivered, how could it be delivered if all available resources were used or if additional resources were developed. Sidel was our advisor during that time."

NEXT UP Although Wegman's investigations among sugar cane workers indicated that interventions reduce the deleterious effects of heat on kidney function, he and his colleagues are studying how the intervention can be improved and how the findings can be generalized. Wegman is also affiliated with several public health professional organizations in which he is promoting the study of occupational hazards that result from changes in climate.

INFLUENTIAL BOOKS *Exploring the Dangerous Trades: The Autobiography of Alice Hamilton, M.D.*, by Alice Hamilton and *Doubt Is Their Product* by David Michaels ■

The Gough-Wentworth technique for preserving tissue from whole organs offered many histopathological advantages: the specimens were durable, portable, and provided a clear view of lesion distribution. This specimen was sent to HMS researchers from Wales more than sixty years ago.

SCIENTIFIC DISCOVERY begets scientific discovery, and Jethro Gough and J. E. Wentworth's foundational paper on preparing entire-organ sections certainly begat its share.

In 1949 the pair of pathologists reported an account of how they obtained, fixed, and mounted on paper thin sections of whole lung from deceased Welsh miners in order to compare the sections with radiographs taken from the miners during life. The authors, and others, considered the paper mounting to be the real innovation of the study.

The original preparation they developed took a total of fourteen days, which included several multistep processes, including fixing, slicing, embedding, drying, and mounting. The fixing step took 48 hours, which some later researchers preserved.

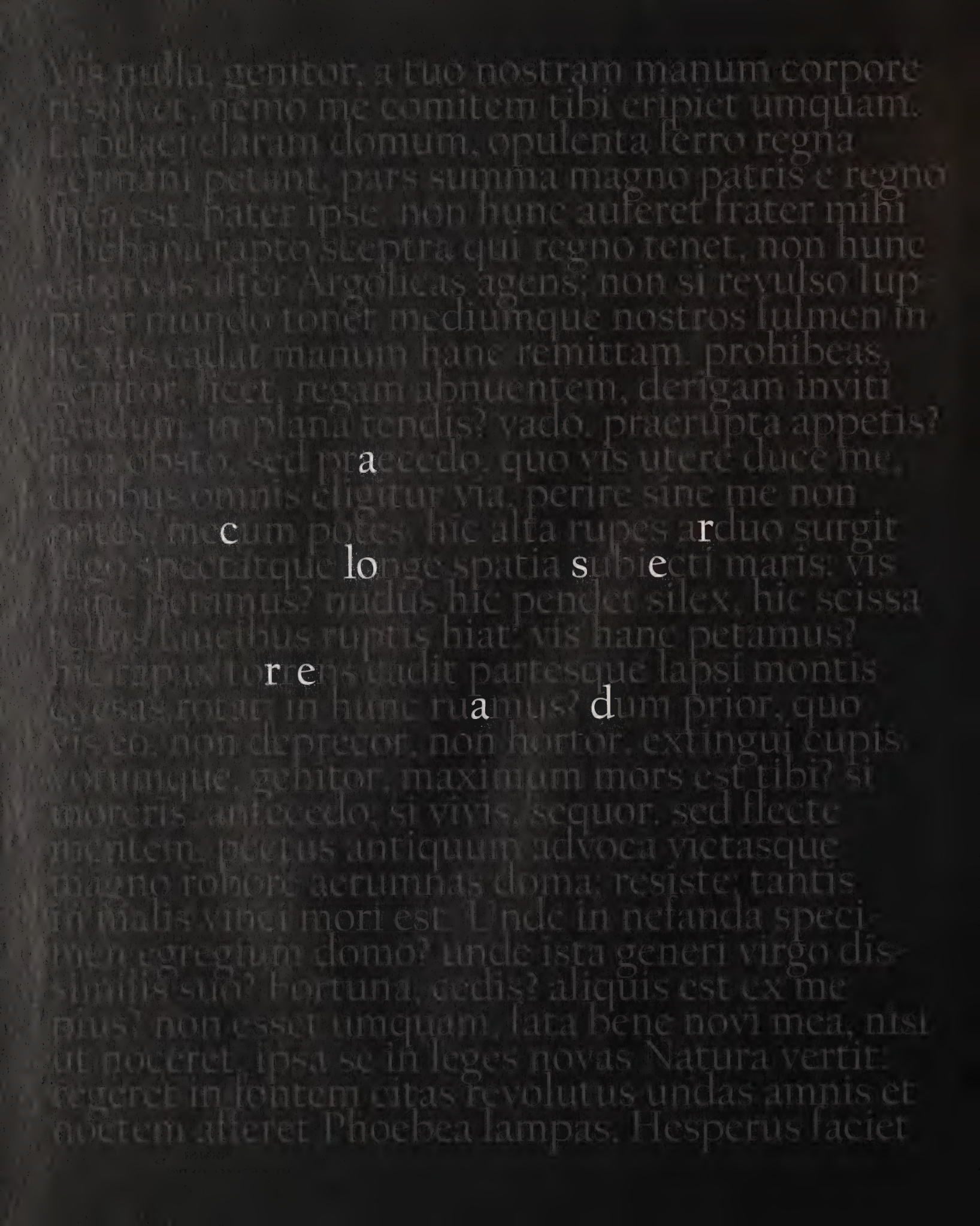
Previously, large pieces of tissue were mounted on glass, which allowed them to be viewed under a microscope. The paper-mounting method made the sections portable and durable.

Researchers from what was then Beth Israel Hospital, Felix Fleischner, HMS clinical professor of radiology, and Leopold Reiner, HMS professor of pathology, used specimens from Gough to study linear x-ray shadows in acquired pulmonary hemosiderosis and congestion, gleaning from them, as they wrote in a 1954 paper, "unparalleled insight into the pulmonary topography."

There have since been improvements and modifications to the Gough-Wentworth technique. In 1969, W. F. Whimster, a pathologist in Jamaica, described a simpler technique that he thought yielded comparable results. His revised process was shorter, too: less than 48 hours for the entire sequence. Whimster also extended use of the method to other organs.

A group in France published its modification in 1993, in which they preserved Gough and Wentworth's fixing time of 48 hours, a period they found acceptable for optimal results, and shortened the subsequent steps more rigorously. Their process produced a section satisfactory for correlating an organ specimen with computed tomography scans for use in histopathological reports, a clinical technique made necessary by the use of high-resolution CT scans to visualize pulmonary anatomy in lung diseases.

Today, the technique to produce rapid giant paper sections of organs is still in use—but not many people know how to do it. John Godleski, an HMS professor of pathology at Brigham and Women's Hospital and a professor in the Department of Environmental Health at the Harvard T.H. Chan School of Public Health, considers Whimster's work the "big step" in advancing the technique, adding that being able to see the pathology and distribution of lesions in slices of whole organs is important for diagnosis, particularly in lung diseases. —*Susan Karcz*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To understand large data sets, researchers look to tools that decipher patterns in natural language

by Kevin Jiang

Joseph Dexter

On a miserably cold January evening in 2014, Joseph Dexter met his friend and mentor Pramit Chaudhuri at a party at a classical studies conference in Chicago. Dexter, a graduate student in the HMS Department of Systems Biology, had met the former Dartmouth classics professor when Dexter, while still in high school, was taking classes at the New Hampshire college. Catching up with one another that evening began with the usual pleasantries, but their conversation soon carried them into uncharted territory. As the night deepened and the room emptied, the pair remained huddled, deliberating an idea: could bioinformatics be adapted for studying ancient literature?

In the first century CE, the Roman philosopher and statesman Seneca—tutor, advisor, and, ultimately, victim of Emperor Nero's anger—wrote a series of plays shaped by the political and social strife of his era. Collectively known as the Senecan tragedies, this corpus was relegated to the margins of history until it was rediscovered by Renaissance scholars in the fifteenth century. The plays' reemergence marked the revival of the tragedy on European stages and served as a model for dramatic traditions that influence Western culture to this day.

The journey of the Senecan tragedies from antiquity to modernity has taken unpredictable turns. But perhaps the unlikeliest detour was made during that late-night conversation, where, over several glasses of wine, a biologist and a classics scholar began to flesh out how techniques from bioinformatics could be used to gain insights about texts such as the Senecan tragedies.

At first blush, it might seem implausible to speculate that ancient Roman plays packed with supernatural intervention and bloodthirsty revenge would have anything in common with the computational analysis of biological data. But for Dexter, whose lifelong obsession with classics paralleled his path to the study of math and biology, and for an increasing number of researchers like him, the intersection of computation, human language, and biology is fertile ground for discovery.

"There are lots of commonalities that arise when you deal with large amounts of multidimensional data in messy, unstructured contexts," he says. "That's certainly true in biomedicine, and it's certainly true in culture and literature."

Driven by rapid growth in computing power and new technologies, almost every facet of biomedical research has been deluged with data in recent years, from the petabyte-sized datasets of "-omic" fields used to study the genome, transcriptome, proteome, and similar molecular entities, to what many are estimating will become the zettabyte-sized data sets of scientific literature and electronic medical records (EMRs).

Extracting meaningful discoveries out of this wealth of information has necessitated the development of tools that not only can identify patterns of interest across massive data sets but can do so despite the inherent "messiness" of biology. This is no simple challenge. Whether at the level of molecules or populations, the study of biological systems involves untangling sets of rules, connections, and interdependencies that have been laid down by evolution that can vary by timing, context, and chance.

Yet computational techniques honed for the study of the complex, interconnected, often ambiguous system we call language are increasingly being used to inform biomedical research. For some applications, these tools are showing enormous promise, from improving our understanding of genomics and biochemical pathways to realizing the full potential of precision medicine.

Dramatic Language

As early as the 1940s, linguists and computer scientists were collaborating on methods that would allow computers to learn, understand, and apply human language to a variety of uses. Known as natural language processing, researchers drew from disciplines such as artificial intelligence, machine learning, computer science, statistics, and computational linguistics to analyze the rules and patterns of language.

As large amounts of linguistic data and increased computing power became available, these efforts bloomed, leading to contemporary applications such as Siri, Apple's intelligent personal assistant software, and Google Translate. The field of biomedical informatics, which leverages similar techniques to analyze and interpret medical and biological data, has similarly matured over the past few decades.

Natural language processing and biomedical informatics intersect in many ways. One of the more unusual examples may be the project launched by Dexter and Chaudhuri after that late-night conversation. Applying a technique they dubbed quantitative literary criticism, the project's team of classics scholars, computer scientists, and computational biologists used computational tools to analyze ancient Latin and Greek texts, including the plays by Seneca.

Earlier this year, Dexter and his colleagues published a paper in *Proceedings of the National Academy of Sciences* in which they used computational profiling of writing style to explore intertextuality—the concept that all texts have relationships to other texts—across the

TOP: LOEB CLASSICAL LIBRARY/SENECA. TRAGEDIES (OPENER); JOHN SOARES (ALL PORTRAITS)

Bioinformatics tools can have powerful and creative applications, but when combined with natural language processing and applied to the biomedical sciences, they have profound implications for human health.

Peter Park and Doga Gulhan

writings of ancient authors. In one trial, they computationally analyzed the entirety of the Senecan tragedies to investigate their influence on a play by a fifteenth-century Italian author writing in the Senecan tradition. The team identified places in which the later play differs in style from plays written by Seneca. By pinpointing these differences, they could reveal various literary effects for which the author was striving and which gave his work its distinctive character.

The group is also pursuing a method for the detection of verbal intertextuality based on one of the most common bioinformatics techniques: sequence alignment. This analysis allows like-to-like comparisons of DNA, RNA, or protein sequences by lining up the molecular strands so that they match at as many locations as possible. In evolutionary studies, this technique has been used to identify similar genes across different species and analyze the degree of difference between them to build phylogenetic trees.

"Linguistics played an important role in the development of sequence alignment tools that are now ubiquitous in biology" says Dexter. "We realized you could use the same techniques on literary problems."

Topic Sentences

Bioinformatics tools can have powerful and creative applications, but when combined with natural language processing and applied to biomedical sciences, they have profound implications for human health.

On the third floor of the Francis A. Countway Library of Medicine, Peter Park, an HMS professor in the Department of Biomedical Informatics, oversees a research group that is using large-scale computational analysis of genomics data to better understand the mechanisms underlying human diseases.

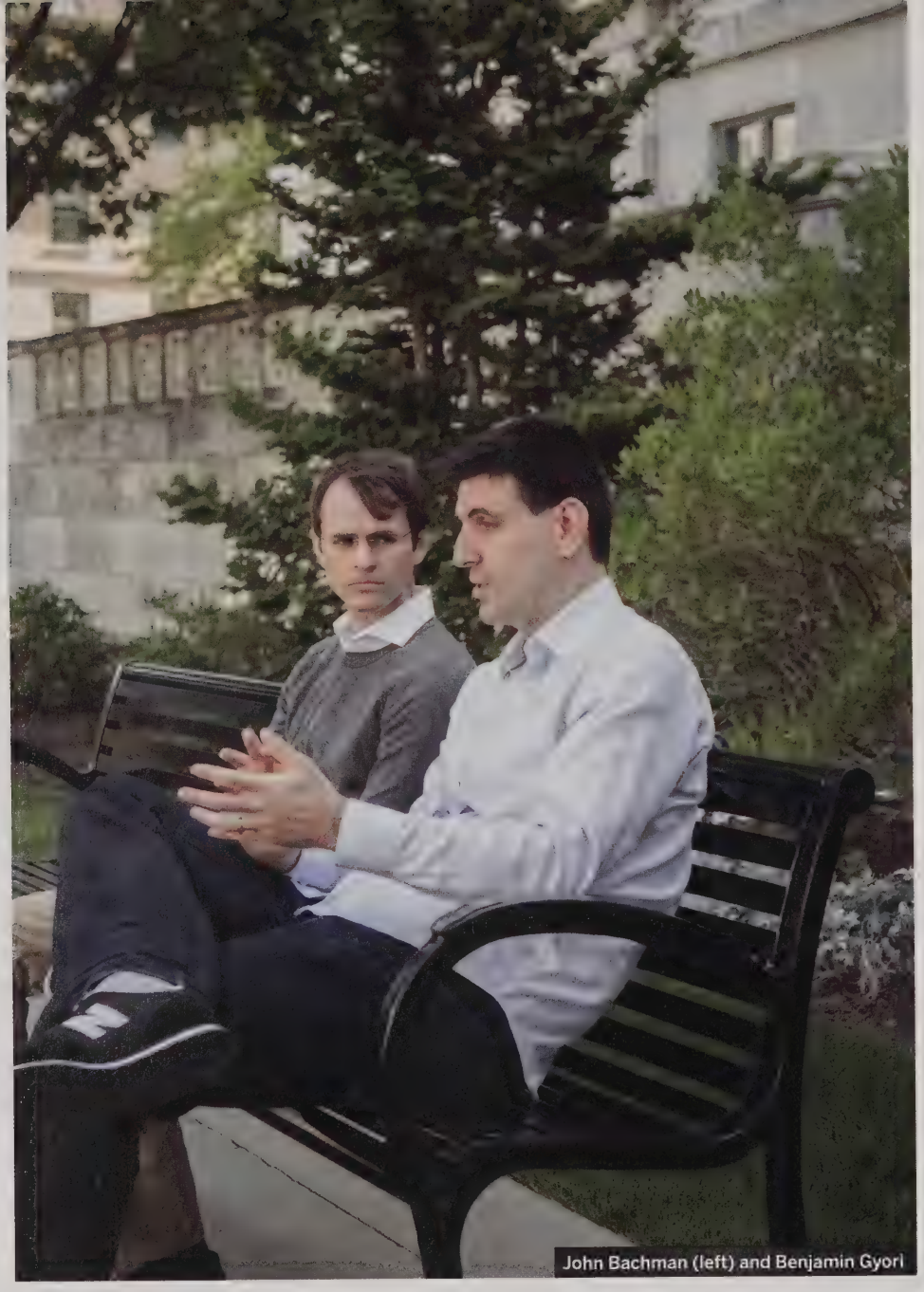
Among the group's many approaches is one drawn directly from natural language processing: a statistical model that can identify what "topics" are contained within texts. Instead of analyzing language, however, Park and his team are identifying the specific causes of mutations in the genomes of cancer patients.

To illustrate with an analogy, a book about military battles of World War I will include the words "tank" and "trench" more frequently than a book about battles in the American Revolutionary War. But both will have more occurrences of words like "gun" and "cannon" than a book about the Punic Wars, which raged in the third through second century BCE.

This technique can be used to scan entire libraries of literary texts for groups of co-occurring words that indicate a common topic. The statistics can then be used to infer not only what the topic of a book may be, but the mixture of topics contained within.

Led by HMS bioinformatics postdoctoral fellow Doga Gulhan—a particle physicist who trained at MIT and worked at CERN—the team applied this concept to genomes. Key to their work are studies that have linked certain causal factors to specific patterns of mutations. In the genomes of smokers, for instance, there is a dramatic increase in cytosine to adenine mutations. These single nucleotide variants are often accompanied by predictable patterns in nucleotides on either side of the single variant.

"If we think of each person's genome as a book that contains many mutations or words," says Gulhan, "we can use our algorithms to find words that occur together and group them by common occurrences into broad topics. You cannot do this using only a few genomes. You need a big set of books so that you can determine what the topics are. Then you can look at each genome to see which topics it contains."



John Bachman (left) and Benjamin Gyori

Park, Gulhan, and their team are scanning trillions of DNA base pairs and petabytes of data found in roughly 2,700 different tumor genome sequences from the International Cancer Genome Consortium. They have identified dozens of mutation signatures that indicate different causal factors, or "topics," in their analogy. Most of these factors are still unknown, but some, including smoking and UV exposure, have been previously identified and are being used to validate and improve the methodology.

"Ultimately, what we want to do is give patients treatments that are appropriate for their disease," Park says. "If you are presented with two tumors, say, a brain tumor and a lung tumor, they might appear to be caused by different factors. But it could be that the same mechanism is causing mutations in both. Sequencing the genomics of cancer patients will soon be a routine practice, and this type of genome analysis will help us sift through the mutations that reflect the history of the tumor, so that we can identify the best drug or combination of drugs to use for the patient."

WALL-E

The tools of natural language processing have shown great promise when applied to biological data, but they are no less valuable within the context of their original intent: to provide computers with the capability to do useful things with human language.

Since 2005, the number of papers and abstracts on biomedical topics indexed by the National Institutes of Health's PubMed search engine has doubled, sitting at somewhere around 27 million, with thousands more being added daily.

"Scientific literature is growing so large that we can't keep up with it all, even within fields," says John Bachman, a research fellow in therapeutic science in the Laboratory for Systems Pharmacology (LSP) and the Harvard Program in Therapeutic Science (HiTS) at HMS. "And it is extremely difficult to know if something relevant to your research might exist in some other field."

In 2014, DARPA, a research and development wing of the U.S. Department of Defense, launched a project to address this growing concern. Dubbed the Big Mechanism program, DARPA tasked research teams with developing computational tools that could intelligently scan and make sense of scientific literature.

To tackle this challenge, a group led by Peter Sorger, the Otto Krayer Professor of Systems Pharmacology at HMS and director of the LSP and HiTS, relied heavily on natural language processing. Led by Bachman and Benjamin Gyori, a research fellow in therapeutic science in the LSP, the team is developing a software platform that reads papers and builds models of complex biochemical networks and can also support interactive dialog with scientists in a manner akin to Apple's Siri.

The platform, named INDRA (the Integrated Network and Dynamical Reasoning Assembler) first uses machine language to parse scientific publications and abstracts to look for phrases of interest. These phrases can include biochemical names and processes, as well as key words, for example, "tumorigenesis" or "metastasis."

"When these systems extract information from the literature, it comes out as this big, error-prone, redundant, fragmented bag of facts," Gyori says. "The main goal of INDRA is to turn those facts into coherent, predictive, and explanatory models. We're not just looking for statistical associations in text, like co-occurrence of a drug name with a disease name. We want to extract causal events."

To do so, the team developed what they're calling a knowledge assembly methodology. INDRA cross-references raw phrases against each other as well as against databases and other knowledge sources in a manner analogous to sequence alignment. Guided by sophisticated algorithms, INDRA eliminates redundant statements and likely errors about biological processes and identifies the mechanisms that connect them.


Alexa McCray

For biomedical researchers to make full use of natural language processing and uncover knowledge that can affect human health and disease, there must be a strong foundation of data built through human effort.

The scale at which INDRA can do this is difficult, if not impossible, for humans to achieve. In one proof-of-concept trial, INDRA assembled a biochemical network model after scanning a corpus of 95,000 papers that contained information relevant to a single study of interest. This study reported on tests involving the efficacy of nearly one hundred drug combinations on melanoma cell lines from which the twenty-two strongest drug effects were selected. The team asked INDRA to find the mechanisms involved. Of the twenty-two observed effects of a drug on a protein, INDRA generated detailed biochemical explanations for twenty, a 90 percent success rate.

With additional natural language processing development, the team has devised a software prototype, provisionally named Bob, that one day will allow any scientist to ask INDRA questions in English and receive an answer in English, basically a virtual lab assistant that can supply information to help researchers formulate and evaluate hypotheses.

Syntax

For patients, tools like INDRA and the topic model used by Park and Gulhan have tremendous potential in opening new lines of research and discovery that can someday affect their health and quality of life. But natural language processing can also have a direct benefit at the bedside.

Perhaps the largest data sets that exist in the biomedical sciences are EMRs, which contain clinical narratives and details such as disease pathology and treatments for hundreds of millions of patients. There is, however, no universal system for EMRs, so they can differ greatly in how critical data elements are presented, from coding for medications to vocabulary use.

This lack of conformity presents an ideal problem for natural language processing tools, one that Guergana Savova, an HMS associate professor and director of the Natural Language Processing Lab at Boston Children's Hospital, may help solve. Savova and her colleagues are building systems that can read and analyze anonymized clinical notes from EMRs and combine that information with other types of information.

One of their efforts is aimed at performing "deep phenotyping" on cancer. Through their analysis of the plain text within millions of EMRs, they hope to reveal the relationships between the characteristics of a cancer, including its molecular profile, grade, and metastasis patterns, and information extracted about patients, such as family histories, tests, treatments, and comorbidities.

"We need to learn as much as we can about these connections if we are to achieve the goal of precision medicine, because every patient and every tumor has a different set of characteristics," says Savova, a computational linguist and computer scientist by training. "These questions can be answered only if researchers have large corpora of data from large cohorts of patients to compare. Manually, it's just not doable."

But state-of-the-art natural language processing systems are not a panacea, and no system is perfect, Savova says. Although errors can be controlled for—INDRA, for example, has a "belief engine" to allow it to determine its probability of correctness—inaccuracies arise for a variety of reasons that range from language variations to the differences in statistical and computational algorithms that underlie any given system.

"We build extraction tools, but there is a tremendous difference between extraction of information and such a complex decision-making process as diagnosis," Savova says. "What a physician observes or hears or feels, the logical and creative steps that humans are capable of, are not necessarily recorded in the EMRs, and they are as important as any amount of text processing. The big question for artificial intelligence in general is how to encode this comprehensive knowledge into one representation."

The vast majority of current-generation natural language processing systems rely on human-initiated resources, such as a list of Latin phrases or biochemical names to search for in a corpus of data or a backbone of medical terms to which clinical notes are connected. This can be a troubling variable.

"There are people who disagree with me,'" says Alexa McCray, a professor of medicine in the Department of Biomedical Informatics at HMS and Beth Israel Deaconess Medical Center, "but if you're working with not-so-good data on the way in, then what comes out the other end is not going to be so good either."

Ensuring access to high-quality data for computational applications has been a priority for McCray for almost her entire career. A linguist who joined IBM as the field of computational linguistics was blossoming, McCray spent decades at the National Library of Medicine at the NIH. There, she helped develop standards such as the Unified Medical Language System, a comprehensive and curated database of millions of biomedical concepts and names. That system now serves as the backbone for many natural language processing applications.

For biomedical researchers to make full use of natural language processing and uncover knowledge that can affect human health and disease, there must be a strong foundation of data built through human effort.

"Data standards, curation, and language processing, these are areas where I think we have to put more of our combined energy," McCray says. "Otherwise, it's the Tower of Babel. What we need to get to is a point where we can compare apples to apples across biomedicine." ■

Kevin Jiang is a science writer in the HMS Office of Communications and External Relations.

FIVE QUESTIONS

FOR JONATHAN ABRAHAM MD '12 PHD '12 ON INFECTIOUS DISEASE

Member of the Faculty, Department of Microbiology and Immunobiology, Harvard Medical School

Clinical research fellow in infectious disease, Brigham and Women's Hospital

What sparked your curiosity in emerging infectious diseases?
The Coming Plague by Laurie Garrett. I read it when I was a senior in high school. It included a chapter on Lassa fever virus in West Africa and described viruses that caused hemorrhagic fevers. I read that book and got hooked. By the time I was a sophomore in college, I had joined a lab that was working on Ebola. I've worked on emerging infectious agents ever since.

How does your work as a clinician inform your work as a basic science researcher?
I've always felt that my experience in clinical medicine inspires the research questions I pursue in the laboratory. I remember thinking hard about how antibodies can be used as infectious disease therapeutics when I was a fourth-year medical student. I was on rotation and saw how well a patient with leukemia responded to treatment with a biomolecule, an antibody-fusion protein. I wondered why we weren't using such therapeutics against infectious agents.

Part of my interest in becoming an infectious diseases doctor grew from my interest in addressing disparities in health care. I come from a Haitian background. When I was growing up, I would hear people say that Haitians were to blame for the U.S. HIV/AIDS epidemic. This drove me to fight such stereotypes. I felt that my best approach was to not only treat patients but also study the mechanisms behind these diseases.

What are the toughest challenges in tackling emerging infectious diseases?
I think the toughest challenge is to move from a reactive state to a proactive approach. We've seen the Zika virus re-emerge. We have seen Ebola and West Nile. One of our more critical challenges is to determine how we can prepare ourselves against whole families of viruses, for example, have one vaccine against Zika and dengue viruses instead of different vaccines against each. The other risk we face is that in certain situations infection by one virus can make subsequent infections by related viruses worse. This is a challenge also in terms of vaccination. We must ensure that the vaccines we develop do not inadvertently enhance infection by related viruses we have not yet encountered.

How do you think climate change is affecting the emergence of infectious diseases?
A lot of troubling diseases are linked to humans' exposure to various vectors, be they mosquitoes or rodents. I think there are precedents suggesting that the destruction of natural habitats and changes in vector habitat ranges caused by climate change could increase our risk of contracting new types of viruses.

What are some of the more pernicious myths about infectious diseases and global health?
There is a lingering idea that our nation's geography will somehow protect us from future outbreaks. I'm glad it's a myth that hasn't yet been disproven, but it is one that makes us vulnerable. We are interdependent and really need to take care of each other. The safest world is one in which everyone is being vaccinated or being treated.

—Ekaterina Pesheva

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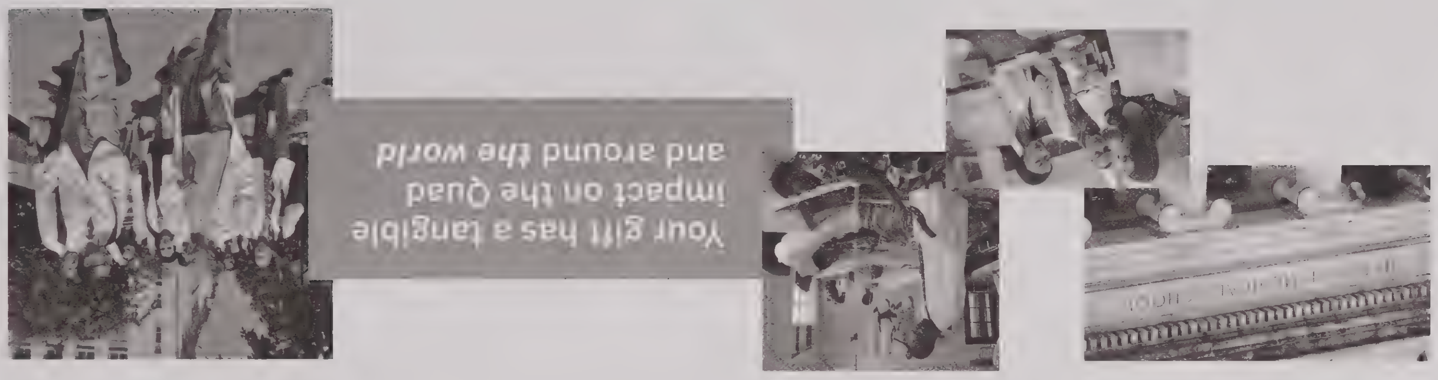

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President's Report

As I write this report, my first as the incoming president of the Harvard Medical Alumni Association and Council, the Longwood Medical Area is humming with the class of first-year students. I just had lunch with several of my current and former advisees and found their brilliance, creativity, kindness, and positive energy both inspiring and humbling. It is truly a privilege to know this next generation of physicians and imagine what they will experience and accomplish in their careers.

Let me briefly tell you what's new with the Council. At our spring meeting, we talked with Ed Hundert '84, dean for medical education; Stephanie Hunt, director of financial aid; and Bob Mayer '69, faculty associate dean for admissions, about some of the challenges we face as we recruit underrepresented minority students.

The School has been reviewing ways it can remain competitive in its ability to recruit top candidates while also honoring its tradition of need-based aid. We also discussed mechanisms to provide additional support for our MD-PhD program, a high priority for Dean George Q. Daley '91.

Dean Daley spoke with the Council about this and other initiatives and acknowledged the Council's contributions and his enthusiasm for working closely with us in the coming years.

The Council took time to carefully consider areas of focus for my two-year term as president. These areas include diversity: develop approaches to ensure that candidates from populations underrepresented in medicine have the opportunity to attend HMS; idealism: identify strategies to enable current students to pursue their ambitions and goals with as little student debt burden as possible; and connection: bringing our remarkable alumni community together across the country and the world to form networks with current faculty, students, and leadership.

At our fall meeting, we welcomed new Council members: Jacqueline Boehme '15, first pentad; Jennifer Mack '98, fourth pentad; Toren Finkel '83, seventh pentad; Robert Barbieri '77; eighth pentad, and Lakshmi Halasyamani '93, councilor-at-large.

We give our heartfelt thanks to members who rotated out of the Council: Michael LaCombe '68, immediate past president; Andrea Reid '88, secretary and councilor-at-large; Carolyn Walsh '09, first pentad; Emily Oken '95, fourth pentad; Richard Payne '77, seventh pentad; and Jean Emans '70, eighth pentad. My special thanks go to outgoing president Jim O'Connell '82. I'm honored to follow him as Council president. The Council looks forward to working closely with Susan Rice, the School's new senior director of alumni engagement. Please let me know if you have comments, ideas, or suggestions. EHenske@partners.org.

Elizabeth (Lisa) Petri Henske '85 is an HMS professor of medicine at Brigham and Women's Hospital, director of the Center for LAM Research and Clinical Care at Brigham and Women's, director of the Brigham Research Institute, associate member of the Broad Institute of MIT and Harvard, and a medical oncologist at the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute.

COURTESY OF ELIZABETH HENSKE; STEVE LIPOFSKY (FAR RIGHT)

Letters of Progress

LGBTQ health elective provides clinical experience

Students participate in an event supporting an end to disparities in health care for members of LGBTQ communities.

WHEN NEAL BAER '96 was attending HMS in the 1990s, he says there were only two students in his class who self-identified as gay and next to nothing was ever mentioned about LGBTQ health.

Following graduation, Baer became a pediatrician, an adjunct professor of preventive medicine at UCLA's Fielding School of Public Health, and an award-winning television writer and producer, working on successful TV shows such as *ER*. Most recently, he has been the executive producer and showrunner of *Law & Order: Special Victims Unit* and *Under the Dome*.

In 2016, Baer returned to HMS to speak to medical and LGBTQ (lesbian, gay, bisexual, transgender, queer and questioning) students. When he asked the students how much exposure they'd had to LGBTQ health issues in medical school, he found that little had changed since his days at HMS; the students still weren't receiving information on how to care for members of these communities.

Fortunately, as the result of efforts by HMS students, the School's education leadership, and Baer himself, things have changed considerably: HMS has introduced an LGBTQ health clinical elective course for its medical students. In addition, Baer has given $250,000 to establish an endowed scholarship to support medical students interested in LGBTQ health.

Since its inception, between five and ten students have taken the class. Neir Eshel '13, is one of them. Now a resident at Stanford University Medical Center, Eshel said he and a few other students began lobbying for broader institutional support for LGBTQ students when they arrived at HMS. In addition, he said, they initiated an extracurricular speaker series with guests who could address LGBTQ health topics. They also began to research LGBTQ health and hold presentations themselves.

The course, Eshel said, was born of many of those efforts.

Robert Kitts, an HMS assistant professor of psychiatry at Massachusetts General Hospital, was instrumental in launching the course and is one of its former co-directors. What makes the HMS course unusual, he says, is that unlike LGBTQ courses at most U.S. medical schools, the School's course places emphasis on clinical experience.

The new elective is a month-long multidisciplinary clinical and scholarly experience that trains HMS students to provide high-quality care to patients who are LGBTQ, gender nonconforming, or born with differences of sex development. The course focuses on having the students work with youth but also provides clinical exposure to and education on working with LGBTQ adults. Clinical settings include psychiatry, adolescent and young adult medicine, pediatrics, family practice, and internal medicine.

Students are asked to demonstrate an ability to elicit sensitive information, recognize individual health risks and challenges, communicate ways to reduce high-risk behaviors, and develop strategies to promote wellness.

—M.R.F. Buckley

Vanderbilt Hall was built in 1927 as a residence hall for HMS students. It was part of a national trend to improve the quality of student life by providing on-campus housing. The original building included a living room, faculty dining rooms, athletic facilities, and a student dining hall, pictured above. Vanderbilt, also known as Vandy, still houses medical students, but its dining hall has been converted to two floors of administrative departments.

Richard Peinert MD '73
This is easy: any time I had a beer in the apartment of **Tom Wright '77**. The best memory was having a beer with about a hundred classmates crammed into Tom's apartment watching the Super Bowl. One of his famous maps has hung in my office for the past 35 years.

Giulio D'Angio MD '45
I have fond memories of my first year in Vanderbilt Hall. I was in a suite with two roommates. We enjoyed the dining hall, which used tablecloths, and the "biddies" who served as waitresses. Then the Army took over. The gentleman's abode was turned into a military barracks with bunk beds, and we Army privates had to line up with trays in the cafeteria.

Our classmates in the Navy retained their officer status as ensigns and suffered none of these strictures. What's more, they delighted in emptying their trash baskets out the windows onto the courtyard, which we then had to clean during our morning policing rounds.

My room was in the deanery, and in the first year one could go down to the kitchen and have a snack. Of course, all of that disappeared under the Army Specialized Training Program. It was wonderful as far as my father was concerned: My $400 tuition, a lot of money in those days, was paid by the government, as were room, board, and supplies.

Mark Perlroth MD '60
The meals with friends.

Charlie Burden MD '59
During our second and third years, my roommate, **Dick Sanderson '59**, and I lived in a fourth-floor suite overlooking Avenue Louis Pasteur and the dormitory parking lot. We had two private bedrooms. We also had a private bath, which we used, except for the bathtub: Since both of us preferred going down the hall and using the area shower, we turned the bathtub into a goldfish pool. The relatively elegant corner living room had a fireplace and a closet in which we did successfully secret a refrigerator.

One late fall day, we conjured up the idea of holding a beach party in the winter, a party that would include toasting marshmallows in the fireplace. The next time we visited my family in Maine, we shoveled sand from Popham Beach into a half dozen 50-pound paper sacks, brought them back to Boston, and lugged them up to our fourth-floor suite. Soon thereafter, on a weekend night, we invited a dozen of our closer friends and their dates to join us for a beach party. We moved the furniture out of the living room, placed mattresses and blankets around the outside walls, and filled the center area with sand. We had a splendid gathering. We held a couple more beach parties that winter before the sand became no longer reusable.

ROUNDS

DETAILS, UPDATES, AND OBSERVATIONS FROM ALUMNI

Kelly Abraham Orringer MD '94
The first-week orientation square dance. How can you beat that? My room was robbed, too. That's not a favorite memory, but it is memorable.

Stanley Bohrer MD '58
It was a day in late April or early May of 1955 or '56. In the early afternoon, snow began to fall, and by late evening, there was more than 20 inches. The streets around Vanderbilt Hall were blocked by cars that had stalled or were stuck. Their occupants were settling in the common rooms of the Hall, as were people who worked in the hospitals and medical centers in the area but couldn't get home. We students helped where we could; we picked up emergency meds from the Brigham for those in need. It was a long night.

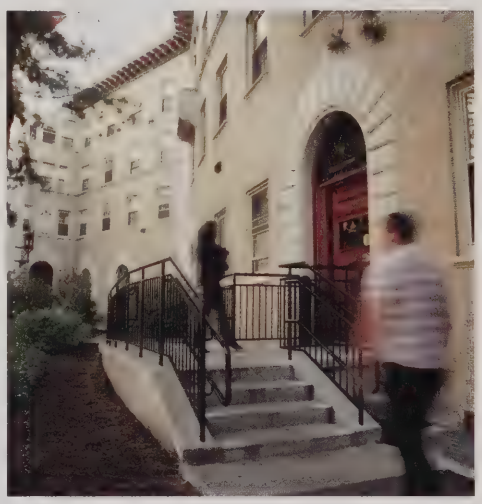
Kathryn Glatter MD '93
We would climb out the window in the kitchen on one of the floors and walk along a narrow ledge on the rooftop. The roof was flat, and you could see Fenway Park; we could watch the Red Sox play for free. It wasn't the safest thing to do, but it was a lot of fun!

Howard Rubenstein MD '57
The collegiality and congeniality. The wonderful conversations in that great dining room over breakfast, lunch, and dinner. And, *mirabile dictu*, having as a street address "Avenue Louis Pasteur." Not a day went by when I didn't gaze at that sign, and what a thrill I got from reading it (but I never prayed to it).

Thomas O'Brien MD '54
Going to the dining hall each evening to eat and talk to friends about whatever.

Martin Lubin MD '45
Students in the Navy could live outside of Vanderbilt Hall. But those in the Army had to live in, even those who, like me, were married. But we found a way down a fire escape and would go home for the night, reappearing for early morning lineup.

The young officer in charge of Army students was disliked, so faculty with clout saw that he was replaced by a jolly, plump senior



obstetrician in the Army, who was immensely popular with both students and faculty.

Michael Rasminsky MD '64
When I arrived in September 1960, I assumed that the second-year student in the room adjacent to mine would be a font of wisdom about all things Harvard. Shaken to learn that he was an Ayn Rand devotee and a dedicated member of the John Birch Society, I sought out the student one door further down the hall, only to discover that these views were shared by this Texan classmate. Happily, I soon learned that this sample of $n = 2$ was unrepresentative and that a hasty retreat to Canada would be unnecessary.

Joan Leary Martinez MD '66
Meals with classmates in the dining hall—and my surprise twenty-third birthday party in my room in the deanery! A friend distracted me by taking me away while others filled my room with balloons! Then we all toasted marshmallows in my room's working fireplace.

David Altshuler MD '90, PhD '90
A group of us played intramural basketball in the Vanderbilt Hall gym, and that relationship continued for decades in the hospitals. It was always fun running into someone on the wards and having a memory of passing them the ball, or (in my case) having them reject your shot.

JOHN SOARES

Sean O'Connor MD '82
The first Cannon Ball, for sure!

Peter Zawadsky MD '68
I spent my first two years in Vanderbilt Hall and liked the convenience of having a dining hall with decent food available three times a day. During my second year I had a room with a working fireplace, which made the room more interesting and livable. I played vol-

leyball as well as squash with several of my classmates on weekends.

Ryan Chuang MD '03
Playing the Steinway piano and first-year fun on the fourth floor.

Edward Ussery MMS '08
I didn't live in Vandy, but there were a number of student activities that I participated in there. After body block, I shared a poem that I had composed with the other first-years. The poem expressed my reflections on the donor who had so graciously allowed me to observe and study incredible things I had never seen before.

Ilonna Rimm MD '81, PhD '83
The blizzard that hit Boston February 5-8, 1978, left 5 feet of snow, 27-foot drifts, and two thousand cars stranded. A state of emergency was called, and HMS closed for several days, an unprecedented action.

In Vanderbilt Hall, the first- and second-year students were marooned, and we were among them. Many of the third- and fourth-year students stayed at the hospital during the storm, caring for patients. Those of us stuck in Vanderbilt agreed that we would have a disco dance every evening until the blizzard was over, which turned into four or five evenings.

ROUNDS

DETAILS, UPDATES, AND OBSERVATIONS FROM ALUMNI

Of course, 1978 was the disco era of John Travolta in *Saturday Night Fever*. Each evening at 7 p.m., a boombox would be brought to the lower-level eating area or the common room, and we would dance. At those parties, many people were just learning to dance; we thought that it was normal that new medical students were just learning. In retrospect, it is quite amazing that so many twenty-two-year-olds did not know how to disco.

Many young HMS students did learn to disco during that blizzard, and some of them, including **Joseph Madsen '80** and I, later married their dance partner.

Ellis Rolett MD '55
Meeting my new classmates, many of whom became lifelong friends.

Joseph Parrish PhD '69
Probably the 1969 classmate I never met—**Michael Crichton MD '69** (*Andromeda Strain*, *Jurassic Park*). The real joyful memory was the shenanigans at the Second Year Show that I produced.

I also taught the biochemistry lab for medical students. Our team project used circular dichroism spectroscopy to determine what nonaqueous fluids could be used to freeze whole blood without denaturing the hemoglobin.

Edward Maynard MD '82
After I moved out of Vanderbilt Hall, **Pam Taylor '82** and I would sneak back to play racquetball in the basement, under the steam pipes. It was the best way to get warm—we couldn't afford to heat our drafty old Victorian in Jamaica Plain.

Calvin J. Collins MD '58
I was married before starting at HMS, so have no memories of days in Vanderbilt Hall. I do, however, have two favorite memories of my days as a medical student at Harvard. One is of my being on the team that wrote and performed the Fourth Year Show. We rehearsed at the Brookline Country Club and were provided with as much beer and as many cigars as we wanted by the Aesculapian alumni. Another memory recalls my fourth-year surgical service at Massachusetts General Hospital. After finishing rounds each Sunday morning, we would go out on the roof of the White building, and, led by chief resident **John Burke '51**, would make paper airplanes and send them sailing toward Storrow Drive.

Thomas A. Waldmann MD '55
In the early 1950s, the Red Scare was at its height; Joseph McCarthy, the junior senator from Wisconsin, was claiming that communists had infiltrated academia in general and Harvard University in particular. The House Un-American Activities Committee, chaired by Rep. Harold H. Velde (R-IL), scheduled open investigational hearings into suspected communist infiltration at Harvard. One hearing was to interrogate a junior member of the Pathology Department at HMS. On the night before the scheduled hearings, and presumably as a protest, someone painted all the toilet seats in Vanderbilt Hall red.

I got up in the middle of the night to use the bathroom and, when flushing the toilet, contaminated an edge of my tennis shoes with red paint. The next day while on a rotation at Massachusetts General Hospital I was summoned to immediately come to the dean's office. When I entered his office, there was Dean George Packer Berry and about a dozen other stern-faced individuals. Prominently displayed on his desk were my tennis shoes, with their apparently incriminating fleck of red paint. The dean said: "We hold you financially and morally responsible for this serious transgression."

I thought my medical career was over before it had started. However, a classmate, **Lester Grant '55**, who had been a medical writer and who was working in the dean's office, assured the dean that I was too much of a grind to have performed the deed. Furthermore, HMS leadership did not want to publicize the red-painted toilet seat incident during such serious times. That would have ended the episode except for a still inexplicable follow-up: someone placed a red jellybean in my Vanderbilt Hall locked mailbox. This continued day in, day out, week in and week out, until spring break, when, at a party in Washington, DC, a little girl, about age two or three, came up to me, handed me a jellybean and said, "Dr. Waldmann, here is your red jellybean." That was the last red jellybean I received.

However, in 2015, at our sixtieth reunion, my classmates insisted that I had done the deed, that I had painted all the toilet seats in Vanderbilt Hall red.

Thanks to all who shared a memory of their days in Vanderbilt Hall.

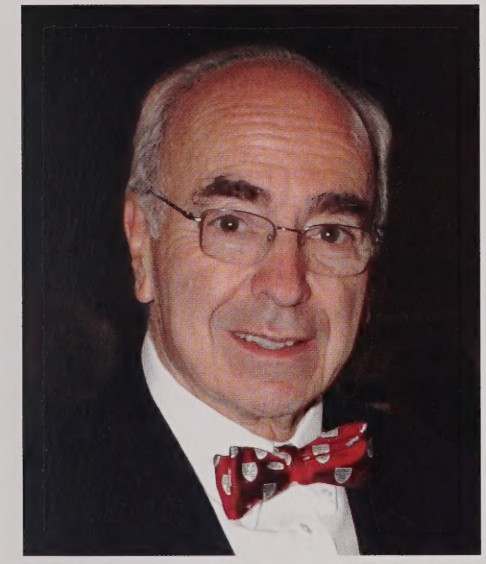
Next up: **Who was your mentor when you were an HMS student, and how did that person's advice guide you?**

Responses can be submitted online at **https://hms.harvard.edu/rounds**, via email at **hmsalum@hms.harvard.edu**; by phone: **617-384-8520**; or by mail: **Rounds, Alumni Affairs and Development, Harvard Medical School, 401 Park Drive, Boston, MA 02215.**

JOHN SOARES

OBITUARIES

REMEMBERING DISTINGUISHED LIVES



Daniel D. Federman 1928 – 2017

DANIEL D. FEDERMAN '53, the HMS Carl W. Walter Distinguished Professor of Medicine and a devoted, cherished, and intensely supportive member of the editorial board of this magazine for twelve years, died on September 6, at the age of 89. Federman loved story, people, and medicine, and put each of those loves to work on behalf of HMS. This magazine's editorial staff is grateful to have had his rich, insightful, and exceptionally inventive contributions throughout the years.

Federman's contributions to medical education, to medicine, and to improving lives everywhere are the stuff of legend. He helped transform medical education at HMS through the New Pathway curriculum and was widely recognized for his research in endocrinology, work that led to his landmark 1967 book, *Abnormal Sexual Development*, which brought together genetics and endocrinology, helping give shape to a new field.

He was, as many longtime members of this community would say, a "triple threat," having graduated from Harvard College '49 and HMS and having done his internship and residency at Massachusetts General Hospital. Except for a brief period as chair of the Department of Medicine at Stanford University, Federman's career was centered at HMS and Mass General.

Following his residency at Mass General, he was appointed to several leadership positions, his first, in 1964, as chief of the hospital's endocrine unit and, ultimately, in 1971, as its associate chairman of medicine. His skill as an educator and mentor led to his appointment as the School's dean for students and alumni in 1977 and, in 1989, he was named dean for medical education. In 2000 he became the senior dean for alumni relations and clinical teaching.

He deeply enjoyed music and continually advocated for incorporating interdisciplinary perspectives from the arts into medicine and medical education, a tradition that continues at HMS today.

Federman was a member of the Institute of Medicine (now the National Academy of Medicine), past chair of the American Board of Internal Medicine, past president of the American College of Physicians, and a founding editor of *Scientific American Medicine*. In 2001, he received the Association of American Medical Colleges' Abraham Flexner Award for Distinguished Service to Medical Education.

Federman's wife, Elizabeth, died in 2008. The Federmans are survived by two daughters, Lise Federman of Boston and Carolyn Federman Zaucha '86 of Chicago; son-in-law, Albert; and three grandchildren.

This listing of deceased alumni includes those alumni whose notices of death were received between June 3 and August 31.

If you know of an alumna/us who has died recently, please email hmsalum@hms.harvard.edu.

1940s

1945

Robert F. Rauch
June 4, 2017

1946

Arthur J. Ourieff
July 4, 2017

1947

Ralph J. Wedgwood
July 23, 2017

1948

Dawson B. Conerly, Jr.
August 16, 2017

Alfred W. Scott, Jr.
July 15, 2017

1950s

1952

Carl H. Cather Jr.
July 3, 2017

Kathleen M. Mogul
August 13, 2017

John J. Turner
August 12, 2017

1953

Charles A. Hamilton
August 19, 2017

Henry G. Ring
May 27, 2017

1954

David L. Collins, Jr.
July 3, 2017

1957

Thomas L. Hall
May 20, 2017

1959

Gene M. Abroms
July 10, 2017

Robert S. Lees
June 5, 2017

1960s

1960

Ben T. Chaffey
May 14, 2017

Carl W. Norden
August 26, 2017

David P. Segel
May 13, 2017

1961

James H. Warram, Jr.
July 5, 2017

1965

John J. McNamara
July 4, 2017

1970s

1971

Robert S. Chapman
August 8, 2017

1975

Edward M. Lukawski
August 8, 2017

1976

Andrea Dlesk
July 7, 2017

1977

Roger F. Steinert
June 6, 2017

1980s

1988

Andrew M. Tager
August 11, 2017

TAKING A HISTORY

PROFILE OF GIULIO D'ANGIO, CLASS OF 1945

CLAIMS TO FAME

Professor Emeritus of Radiation Oncology, Hospital of the University of Pennsylvania; past president, International Society of Pediatric Oncology and founder of the first Late Effects Study group; founder of the Histiocyte Society, the Society for Paediatric Radiology, and the Paediatric Radiation Oncology Society

ITALIA

Giulio D'Angio grew up in Brooklyn and Westchester County, New York, but it was 1929, the year he was seven years old and his family lived in Italy, that, he says, left an indelible mark regarding this nation's chauvinism. Although he took classes in geometry, history, art, arithmetic, and several languages, when he returned to PS 201 in Brooklyn, he was put back a year. The reason? "What could I possibly have learned in Italy?"

PREP TIME

While at HMS, D'Angio sensed that his destiny was to work with children. He trained at what was then known as Children's Hospital in surgery under Robert E. Gross '31, a pioneer in pediatric heart surgery; and in radiology under Martin "Dick" Wittenborg, a mentor who taught him to look at an x-ray as a film clip from a movie: "when looking at the image in front of you, think about what came before and what's going to happen after."

FAMILY PRACTICE

Another strong influence was his work in a lab with Sidney Farber '27, founder of the Children's Cancer Research Foundation, the precursor to the Dana-Farber Cancer Institute. From Farber, D'Angio learned an abiding lesson: when you have a sick child, you have a sick family. The physician must consider how the family is altered by the child's illness, how suffering is shared, and how expenses mount.

When parents would bring in their sick child with their other children, D'Angio says he would make a point of addressing the siblings first, complimenting them or showing an interest in something they were wearing or playing with. He would also thank them for helping their parents care for their sick sister or brother.

LOOKING AHEAD

As a clinician, D'Angio focused on making treatment regimens more family-friendly and on monitoring the long-term effects of cancer treatment. Believing that "cure is not enough," a slogan D'Angio coined, he researched the late effects of cancer treatment in children. What, he asked, would life be like for the child 20 years after treatment? How can that outcome be improved?

SUNNY SIDE UP

Exhibiting a special kind of optimism, D'Angio says that during his long career in pediatric oncology, he never met a nasty person in a professional capacity. People in pediatrics, he says, tend to pull together to help make things better for children.

Bringing this optimism to his patients, D'Angio championed the concept of "total care," a term he credits Farber for originating. D'Angio saw a need to coordinate a child's care and thus right a wrong he saw in practice—compartmentalization of care. He is proud of his ability to get disparate specialists to talk to one another, to create a unified team to solve a common problem: how to make a sick child well.

When he served as chair of the National Wilms Tumor Study, he brought along this concept. In the 1980s, the study addressed psycho-socio-economic issues of treatment, showing that survival results were not impaired if treatments were curtailed in frequency and overall duration.

"The benefits to harried families," he says, "and to health care teams, were incalculable—a gain for society overall."

—Susan Karcz

HARVARD
MEDICAL SCHOOL

"I work with the faculty, students, staff, and researchers at Harvard Medical School. So it is a privilege to give to an institution I know well."

— Lisa Mayer, EdM '81
Executive Director, Giovanni Armenise-Harvard Foundation

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WHAT WILL BE YOUR LEGACY?

Lisa Mayer has worked at HMS for 17 years. Her deferred gift annuity establishes a teaching and research fund to support the HMS Family Van, a mobile health clinic. She will receive fixed income for life, with payments postponed until she needs them.

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